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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 XIV-Reports in 2007

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Abstract

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

Number XIV- Reports in 2007

Adverse events following immunization (AEFI) in the National Vaccination Programme of the Netherlands (RVP) have been monitored through an enhanced passive surveillance system 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. An RIVM expert panel continued the reassessment of selected adverse events from 2004 onwards. Reports were received mainly from Child Health Care professionals, primarily by telephone through the operating service for information and advice on vaccines and vaccinations. Further data have been obtained, if necessary, from parents, general practitioners, paediatricians and other professionals. After supplementation and verification of data a (working) diagnosis is made and causality assessed. In this annual report on 2007 an overview of all reported AEFI is presented with classification according to case definitions and causality. Trend analysis, reporting bias, background rates of specific events and possible pathophysiology of symptoms are discussed. On a total of over 1.4 million vaccination dates 995 AEFI were reported. In 72% (710) of the classifiable events a possible causal relation with vaccination was established. These concerned major adverse reactions in 50% and minor adverse reactions in 50% of the reports. Of the reported adverse events 28% (280) were considered chance occurrences.

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

Rapport in het kort

Postvaccinale gebeurtenissen binnen het Rijksvaccinatieprogramma

Deel XIV- Meldingen in 2007

De bijwerkingenbewaking van het Rijksvaccinatieprogramma over 2007 liet een duidelijke afname zien van het aantal meldingen. In 2007 zijn in totaal 995 meldingen ontvangen. Hiervan werd 72% als bijwerking van de vaccinaties beschouwd. De rest (28%) was niet door de vaccinatie veroorzaakt. Het aantal bijwerkingen moet in relatie worden gezien tot de 1,4 miljoen vaccinatiemomenten en de bijna 7 miljoen vaccincomponenten die daarbij worden toegediend.
Het Rijksvaccinatieprogramma (RVP) wordt sinds 1962 intensief bewaakt. De meldgraad van vermoede bijwerkingen is hoog met een goede meldbereidheid van de consultatiebureaus. Er is een relatief beperkte onderrapportage. Van de 995 meldingen betrof het in 710 (72%) gevallen een bijwerking. Hierbij ging het in 54% om heftiger verschijnselen, vooral zeer hoge koorts, langdurig huilen, collapsreacties, verkleurde benen, koortsstuipen en atypische aanvallen met rilligheid, schrikschokken en gespannenheid of juist een heel slappe houding. Hoewel al deze bijwerkingen omstanders erg kunnen laten schrikken, zijn ze medisch gezien niet gevaarlijk en laten ze geen restverschijnselen na. Bedreigende allergische reacties zijn niet gemeld. De ernstige infecties die werden gerapporteerd hadden geen relatie met de vaccinaties en datzelfde gold voor de meldingen van epilepsie of suikerziekte. Het ging hierbij om een toevallige samenloop van gebeurtenissen. Bij de vier meldingen van overleden kinderen is het overlijden niet door de vaccinaties veroorzaakt.
De gestimuleerde passieve veiligheidsbewaking is een goed en gevoelig instrument om signalen over mogelijke bijwerkingen op te pikken; het systeem laat tevens follow-up onderzoek toe.
Hoewel heftige bijwerkingen na de RVP-vaccinaties optreden, zijn ze van voorbijgaande aard en leiden ze niet tot blijvende gevolgen. De grote gezondheidswinst die het RVP oplevert, weegt op tegen de bijwerkingen.

Trefwoorden:
bijwerking, Rijksvaccinatieprogramma, veiligheidsbewaking, vaccinaties, RVP

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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)
DPT-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
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)
PEA	Provincial Immunization Administration (registry)
PMS	Post Marketing Surveillance
RIVM	National Institute for Public Health and the Environment
RVP	Netherlands Vaccination Programme
SAE	Serious Adverse Event
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. RIVM reports fully, on all incoming reports in a calendar year, irrespective of causal relation, since 1994. This report on 2007 is the fourteenth annual report.
The majority of reports (92%) came in by telephone. Child Health Care professionals are the main reporters (89%). Parents, GP's and/or hospital provided additional data on request (92%). RIVM made a (working) diagnosis and assessed causality after supplementation and verification of data.
In 2007, on a total of over 1.4 million vaccination dates, 995 AEFI were submitted, concerning 914 children. Of these only five were not classifiable because of missing information. Of the classifiable events 710 (72%) were judged to be possibly, probably or definitely causally related with the vaccination (adverse reactions) and 280 (28%) were considered coincidental events.
So-called "minor" local, skin or systemic events were assessed in 554 cases with 356 reports (65%) 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 some local reactions) occurred in 441 cases. In 81% (354) these were considered possible adverse reactions. Discoloured legs were reported 81 times with possible causal relation in all but four. Collapse occurred 96 times, in only 17 cases without causal relation. Fourteen breath holding spells were reported, all with inferred causality and 31 times fainting in older children. Convulsions were diagnosed in 45 cases, in all but three with fever. Of the convulsions 33 were considered causally related. Atypical attacks (18) had possible causal relation in 10 cases. Epilepsy (6) was considered chance occurrence in all instances. Of persistent screaming 41 out of 42 reports were considered adverse reactions. Fever of ≥ 40.5 °C was the working diagnosis in 41 reports of the major-illness category, in all but seven with inferred causality. Of the other 32 major-illness cases five had a possible causal relation. These events were "vaccinitis" (2) all with very high fever (≥ 40.5 °C) and ITP (3). There were five abscesses, all occurring after DTP-IPV-Hib and PCV7. One case of encephalopathy/-itis was reported in 2007, not induced by the vaccination but considered coincidental.
In 2007 all four reported deaths were considered chance occurrences after thorough assessment. One child was examined post mortem. One child had several periods of apneu, EEG abnormalities and bronchopneumonia, one child had pre-existent epilepsy and encephalopathy. Two children were diagnosed as clinical SIDS, because no autopsy was performed and there was no plausible explanation for the death.
Most frequently (672) reports involved simultaneous vaccination against diphtheria, pertussis, tetanus, polio, *Haemophilus influenzae* type b infections (DTP-IPV-Hib, sometimes combined with Hepatitis B vaccine) and seven valent conjugated pneumococcal vaccine (PCV7). Measles, mumps and rubella (MMR) was involved 233 times, 215 times with simultaneous other vaccines, most often DT-IPV or conjugated meningococcal C vaccine (MenC). In 63% of these reports there was possible causal relation with the vaccination(s). For the other vaccine combinations this was 75%.
In 2007 the number of reports decreased compared to 2006, not fully explained by a decreasing birth cohort. The decrease is most prominent seen following MMR and MenC vaccination. Perhaps the temporarily change to a MMR from a different manufacturer has played a role in this decrease.
The total of 995 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 events 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 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 2007. 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 2007 and compare them with previous years. In 2007 the programme was similar to 2006, 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.

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2 The Vaccination 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 2007

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 at the Provincial Immunization Administration (PEA).[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 Medical Consultant of the PEA (MAE) 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 2007 are 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 2006-2007 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 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] 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.[29]

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).[2,30,31]

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 Vaccination 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 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, etceteras.
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 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 RIVM.

3.12 Medical control agency and pharmacovigilance

RIVM and Netherlands Pharmacovigilance Foundation (Lareb) exchange all reported adverse events on the RVP, thus allowing the Dutch medical control agency (CBG) to fulfil its obligations towards WHO and EMEA.

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4 Results

4.1 Number of reports

In 2007 RIVM received 995 notifications of adverse events (Table 1). This is a statistically significant decrease compared to 2006. Since 2005 the number of reports 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. Also we added the seven valent pneumococcal conjugate vaccine (PCV7) to the programme for children born from April first onwards.[28] In the year under report the RVP did not change. For the period 1994 up to 2004 inclusive, a period 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.

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

year of notification	total
1994	**712**
1995	800
1996	732
1997	822
1998	**1100**
1999	1197
2000	1142
2001	**1331**
2002	1332
2003	1374
2004	**2141**
2005	**1036**
2006	**1159**
2007	**995**

The 995 notifications of 2007 involved 914 children. 53 Notifications were multiple, resulting in 107 reports. 22 Notifications were compound. 2 notifications were compound and multiple, resulting in 7 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 2002-2007

notifications 2007	children	adverse event reports	reports 2006	2005	2004	2003	2002
single	837[a]	837	967	890	1756	1166	1174
multiple	53[b]	107	116	99	280	151	111
compound	22[c]	44	66	44	80	41	34
compound and multiple	2	7	10	3	25	16	13
Total 2007	914	995	1159	1036	2141	1374	1332

[a] 15 children had also reports in previous (13) or following (2) years; these are not included
[b] one child with triple reports
[c] all children had double reports

The reports per month showed dispersion/changeability, similar to previous years (Figure 1).

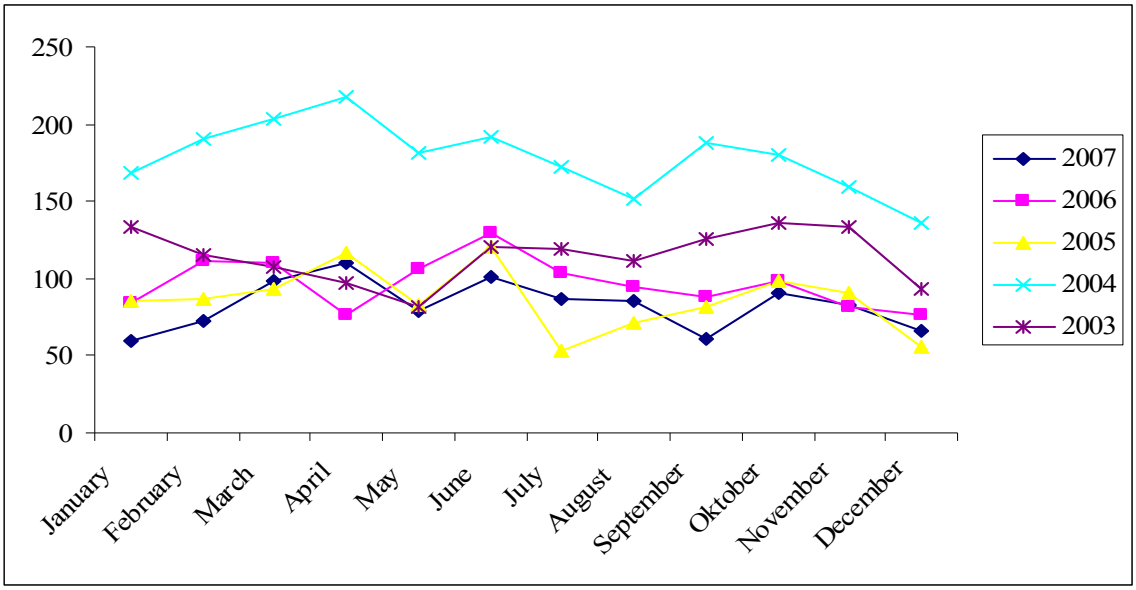

Figure 1: Absolute numbers of reports per month in 2003-2007

4.2 Reporters, source and route of information

Child Health Care professionals accounted for 845 reports (85%). In 2002-2006 this varied between 82% and 85%. In 98 reports (9.8%), parents were the primary reporters (range 8.2%-12.6% in 2002-2006). The share of other report sources also was more or less stable (detailed information in Figure 2 and Table 3).

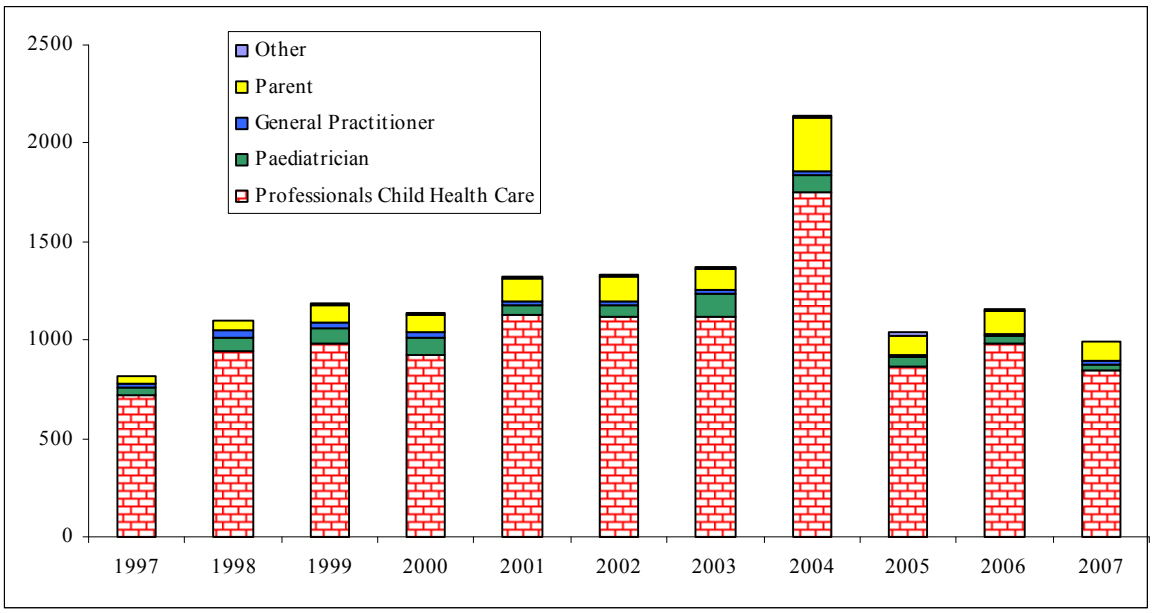

Figure 2. Reporters of adverse events following vaccinations under the RVP 1997-2007

As in previous years the vast majority of reports reached us by telephone (Table 3). We received 77 (7.8%; range 4.9%-12.9% for 2002-2006) written reports, including 38 reports by email and two reports by fax..

Table 3. Source and reporting route of AEFI in 2002-2007

		2002	2003	2004	2005	2006	2007
Child Health Care	Child health clinic	1073	1078	1685	775	894	777
	Municipal health service	39	39	44	76	80	50
	District Consultant	8	5	21	12	8	18
Paediatrician		61	108	84	48	35	33
General Practitioner		17	22	24	13	11	15
Parent		121	113	271	102	121	98
Other		13	9	12	10	10	4
Unknown		-	-	-	-	-	-
total		1332	1374	2141	1036	1159	995
(% written)		(4.9)	(7.9)	(12.9)	(11.3)	(9.6)	(7.8)

In 2007 the reporter was the sole informer in 12%. Additional information was received in 88%, both spontaneously and requested (range 72-88% for 2002-2006). Professionals of Child Health Care supplied information in 88.7%, compared to 91.2-94.5% in the previous five years. Parents were contacted in 92.4%, (range 76%-91% for 2002-2006). Reports in which the parents were the sole informers (59) are included. Hospital specialists supplied information in 17% of the reports (range 16%-24% for 2002-2006). See for details Table 4.

Table 4. Information source and type of events in reported AEFI in 2007

info ⇒	clinic*	+	+	+	+	+	+	+	+	-	-	-	-	-	-	Total	(%)
	parent	-	+	+	+	+	-	-	-	+	+	+	-	-	-	883	(88.7)
	gen. pract.	-	-	-	+	+	-	+	+	+	-	-	+	-	-	919	(92.4)
	hospital	-	-	+	-	+	+	-	+	-	+	-	-	+	-	42	(4.2)
event ⇓	other	-	-	-	-	-	-	-	-	-	-	-	-	-	+	166	(16.7)
																3	(0.3)
local reaction		7	6	3	3	-	-	1	-	6	2	7	-	-	-		93
general illness	minor	1	2	2	6	3	2	4	-	4	4	3	2	3	3		390
	major	2	3	1	1	-	5	-	-	-	1	1	-	1	-		73
persistent screaming		1	3	-	-	-	-	-	-	-	-	2	-	-	-		42
skin symptoms		6	6	7	5	-	1	1	-	2	4	8	-	1	-		101
discoloured legs		1	6	1	-	-	-	-	-	-	1	4	-	-	-		81
faints		1	9	2	-	1	-	-	-	-	5	6	-	-	-		141
fits		-	3	2	3	-	3	-	-	-	4	1	-	-	-		69
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-	-		-
encephalopathy/-itis		-	-	-	-	-	-	-	-	-	-	-	-	1	-		1
death		1	-	1	-	-	2	-	-	-	-	-	-	-	-		4
total 2007		4	6	1	1	4	1	6	-	1	3	5	2	6	3		995

4.3 Sex distribution

In the current year 54% of the reported cases were male, in line with the national distribution. For the years 2002-2006 this ranged between 51-54% (Table 5). Of five children the sex is not known.

Table 5. Events and sex of reported AEFI in 2002-2007 (totals and percentage males)

event ⇓	sex⇒	m%	2002 total	m%	2003 total	m%	2004 total	m%	2005 total	m%	2006 total	m%	2007 total
local reaction		43	120	49	123	48	129	46	93	51	102	54	93
general illness	minor	53	417	57	460	56	704	55	389	52	403	56	390
	major	52	112	57	119	53	194	52	97	47	111	62	73
persistent screaming		61	46	56	55	50	133	47	58	54	61	55	42
skin symptoms		51	104	51	104	53	106	49	82	54	97	55	101
discoloured legs		51	137	42	134	53	279	51	57	50	124	51	81
faints		52	270	49	210	54	318	51	75	50	169	53	141
fits		58	45	53	70	56	98	53	71	47	85	48	69
anaphylactic shock			-	-	-	-	-	-		-	-	-	-
encephalopathy/-itis			-	-	-	0	3	100	1	100	1	0	1
death		75	8	100	3	25	4	38	8	83	6	75	4
total		52	1332	52	1374	54	2141	52	1036	51	1159	54	995

4.4 Vaccines and adherence to the programme

In the current year 94% of the notifications concerned recent vaccinations. Some of the 55 late reports arose from concerns about planned boosters or vaccination of younger siblings. In Table 6 scheduled and actually administered vaccines are listed. According to previous years (except 2005) reports on the first DTP-IPV-Hib and PCV7 dose were the most prevalent. For all doses except the first and third, the number of reports decreased. Most prominent the decrease was seen in reports following MMR and MenC.

Table 6. Schedule and vaccines of reported AEFI in 2007

vaccine given⇒ scheduled ⇓	dtp-ipv + pneu	dtp-ipv-hib	dtp-ipv-hib+ hepb	dtp-ipv-hib+ pneu	dtp-ipv-hib+ hepb + pneu	mmr	mmr men c	dt-ipv	dtp-ipv	dt-ipv mmr	other	total 2007	2006	2005	2004	2003	2002
at birth	-	-	-	-	-	-	-	-	-	-	-		-	-	2	-	-
dose 1[a]	5[l]	19[b]	1	248	23	-	-	-	-	-	-	296	285	205	725	462	503
dose 2[a]	2[c]	7	-	117	19	-	-	-	-	-	-	145	195	153	379	229	212
dose 3[a]	3[d]	1	1	97	15	-	-	-	-	-	1	118	99	111	289	147	150
dose 4[a]	-	29[e]	8[b]	58[f]	15	-	-	-	-	-	2	112	154	119	340	193	161
dose?	-	-	-	-	1	-	-	-	-	-	-	1	1	3	3	3	5
mmr0	-	-	-	-	-	4	-	-	-	-	-	4	7	10	1	8	-
mmr1+menC	-	-	-	-	-	15[h]	156[i]	1	-	-	2	174	226	246	225	173	150
dtp-ipv5	-	-	-	-	-	-	-	6[j]	71[b]	-	3	80	98	114	90	78	67
dtp6+mmr2	1[g]	-	-	-	-	-	-	3	-	57	1	62	88	62	62	37	35
menc	-	-	-	-	-	-	-	-	-	-	-	-	-	5	19	34	38
other	-	-	-	-	-	-	-	2[k]	-	-	1	3	6	8	6	10	11
total 2007	11	56	10	520	73	19	156	12	71	57	10[m]	995	1159	1036	2141	1374	1332

[a] usually DTP-IPV-Hib is administered, simultaneously with pcv7. DTP-IPV-Hib-HepB is given to children of HBsAg carrier mothers and to children with one parent born in a HepB medium or high endemic country concurrently with pcv7.
[b] once with menC
[c] only pcv7
[d] once only dtp-ipv
[e] twice with menC and twice with mmr
[f] once with mmr
[g] only hib with menC and pcv7
[h] once with pcv7
[l] once with hepAB, twice menC only
[j] once with hib
[k] once with hepA, once with hepB
[l] once with menC, three times pcv7 only
[m] once rotavirus, twice bcg, once T+Tig, twice hepB, twice hepA, twice influenza

The relative frequencies of involved vaccinations changed a little compared to previous years. After the introduction of DTP-IPV-Hib with an acellular pertussis component, the number of reported adverse events after DTP-IPV-Hib doses fluctuates at a lower level compared to the period of whole cell

pertussis. See for information on reporting rates per dose section 4.5. Further details in Table 6 and Figure 3.

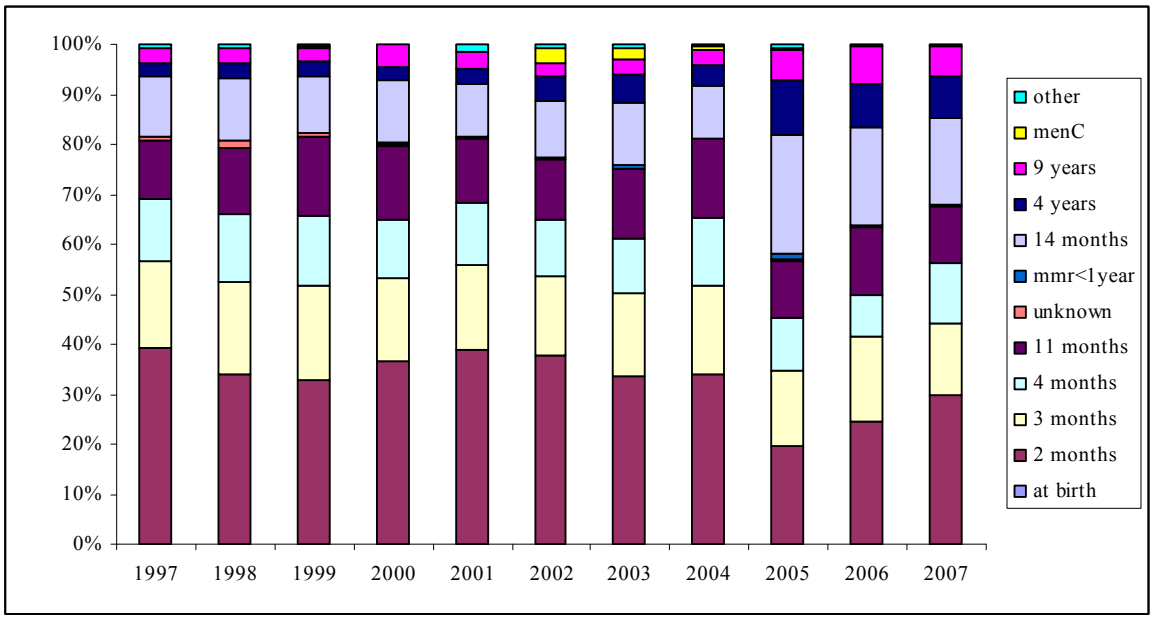

Figure 3. Relative frequencies of vaccine doses in reported AEFI in 1997-2007

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 6% of the reports concern vaccinations, administered more than one year before reporting. Compared to the two previous years, reports contain more aberration from the RVP schedule (Figure 4).

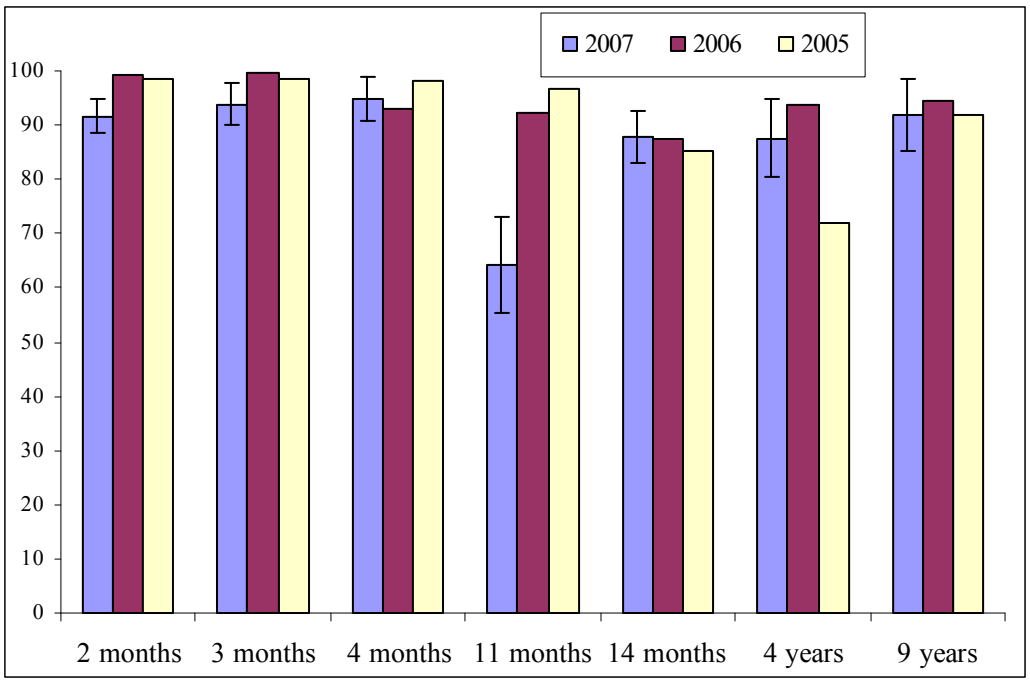

Figure 4: percentage adherence to the RVP schedule among reports of AEFI per dose for 2005-2007.

Reporting rates

Reports were not evenly spread by region and dose. Standardisation of these rates per 1000 vaccinated infants is done according to coverage data from the PEA. Rates were calculated with vaccination coverage data of Praeventis, the new 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 yearly to 187,910, 185,057 and 180,882 in 2005, 2006 and 2007, respectively (www.statline.nl). The regional reporting rate was 5.5 per 1000 vaccinated infants (DTP-IPV-Hib3) in 2007. Range for 2002-2006 is 5.7-11.5 (DTP-IPV-Hib3). There was more dispersion of the reporting rates over the different regions, compared to 2006.

Table 7. Regional distribution of reported AEFI in 2002-2007, per 1000 vaccinated children[a] with proportionate confidence interval for 2007 (major adverse events). Figures not containing overall reporting rate in red.

	2002 (major)	2003 (major)	2004 (major)	2005 (major)	2006 (major)	2007 (major)	95% c.i. 2007 (major)
Groningen	4.1 (2.5)	5,4 (2.8)	16.4 (9.8)	6.7 (2.5)	7.4 (3.7)	4.9 (2.3)	3.1-6.8 (1.1-3.5)
Friesland	7.6 (4.8)	7,5 (4.4)	13.1 (7.7)	5.1 (3.0)	5.8 (3.0)	4.1 (2.3)	2.7-5.6 (1.2-3.4)
Drenthe	3.1 (2.2)	6,3 (3.7)	12.6 (10.1)	5.3 (2.7)	5.3 (2.7)	2.5 (1.3)	1.1-3.8 (0.3-2.3)
Overijssel	6.4 (3.7)	7,5 (3.3)	11.2 (5.8)	4.2 (1.6)	6.9 (3.5)	6.1 (2.8)	4.7-7.4 (1.9-3.7)
Flevoland	6.8 (3.4)	7,3 (4.2)	16.3 (9.1)	8.7 (3.7)	6.0 (2.5)	4.8 (1.4)	2.9-6.7 (0.4-2.4)
Gelderland	5.9 (3.2)	6.4 (3.0)	10.8 (5.8)	5.8 (2.4)	6.1 (2.9)	5.7 (2.5)	4.7-6.7 (1.8-3.1)
Utrecht	6.7 (3.1)	6,9 (3.3)	8.1 (4.9)	8.1 (4.6)	8.6 (5.6	7.3 (3.2)	6.0-8.7 (2.3-4.1)
Noord-Holland[b]	4.2 (2.3)	4.8 (2.4)	9.3 (5.2)	5.0 (2.5)	5.6 (3.0)	4.7 (1.8)	3.8-5.6 (1.2-2.3)
Amsterdam	6.0 (2.6)	7.0 (3.8)	9.8 (4.1)	5.4 (2.1)	6.7 (3.5)	4.6 (1.8)	3.2-6.0 (0.9-2.7)
Zuid-Holland[b]	7.6 (3.8)	8.7 (4.7)	11.8 (6.4)	5.2 (2.5)	6.5 (2.9)	5.7 (2.4)	4.8-6.6 (1.8-3.0)
Rotterdam	5.6 (2.4)	4,6 (1.6)	6.6 (4.7)	3.7 (1.9)	4.6 (2.1)	3.2 (1.4)	1.8-4.6 (0.5-2.4)
Den Haag	6.1 (2.5)	10.0 (5.7)	9.5 (5.8)	5.8 (1.9)	4.2 (1.6)	7.0 (3.7)	4.8-9.1 (2.1-5.2)
Zeeland	7.1 (5.6)	8.4 (3.9)	14.1 (10.7)	4.1 (1.6)	5.2 (2.7)	5.7 (2.5)	3.3-8.2 (0.9-4.1)
Noord-Brabant	8.5 (4.8)	7,8 (4.2)	14.5 (8.5)	6.8 (3.3)	7.1 (3.6)	6.8 (3.2)	5.8-7.8 (2.5-3.9)
Limburg	10.3 (5.3)	8.6 (4.6)	12.0 (6.8)	5.2 (2.9)	6.2 (2.7)	4.0 (2.3)	2.8-5.3 (1.3-3.2)
Netherlands	6.7 (3.6)	7.2 (3.7)	11.5 (6.6)	5.7 (2.7)	6.4 (3.2)	5.5 (2.4)	5.2-5.9 (2.2-2.7)

[a] for 2002 until 2005 included coverage data of the corresponding year out of Praeventis have been used; data of 2005 are applied to 2006 and 2007 as well, because definite numbers were not available.

[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 10 of the 15 regions. The country's average reporting rate for major events is 2.4/1000. Range for 2002-2006 is 2.7-6.6. One region had a higher reporting rate for major events only and two regions a lower. We will present and compare differences in numbers of specific events in the respective sections under 4.9. For more information see Table 7.

For 2006 and 2007 rates mentioned above are an underestimation of the real reporting rates, due to a decreasing birth cohort. However, vaccination coverage is very stable.[5] Therefore we applied the coverage data of 2005 on the actual birth cohorts of 2006 and 2007. See table 8 for the corresponding reporting rates. For reporting rates per dose and per category we also used data of the actual birth cohort.

Table 8: Reporting rates total and of minor and major events in 2005-2007, per 1000 vaccinated children[a] with proportionate confidence interval for 2007.

	2005	2006	2007	95%CI
minor events	3.0	3.2	3.2	2.9-3.5
major events	2.7	3.3	2.5	2.3-2.8
total	5.7	6.4	5.7	5.4-6.1

[a] actual birth cohort used with vaccination coverage of 2005

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.

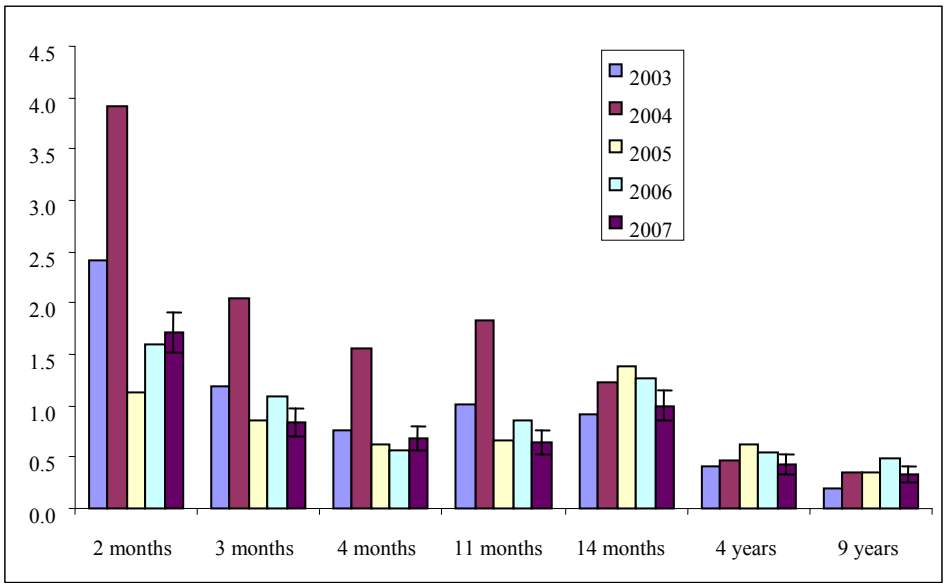

Figure 5: Reporting rate per dose per 1000 vaccinated children

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 441 of 995 (44.3%), compared to 50.5% and 47.3% in 2006 and 2005, respectively. For 1997 till 2004 included the share of major events ranged from 51.5%-57.3% (Figure 6).

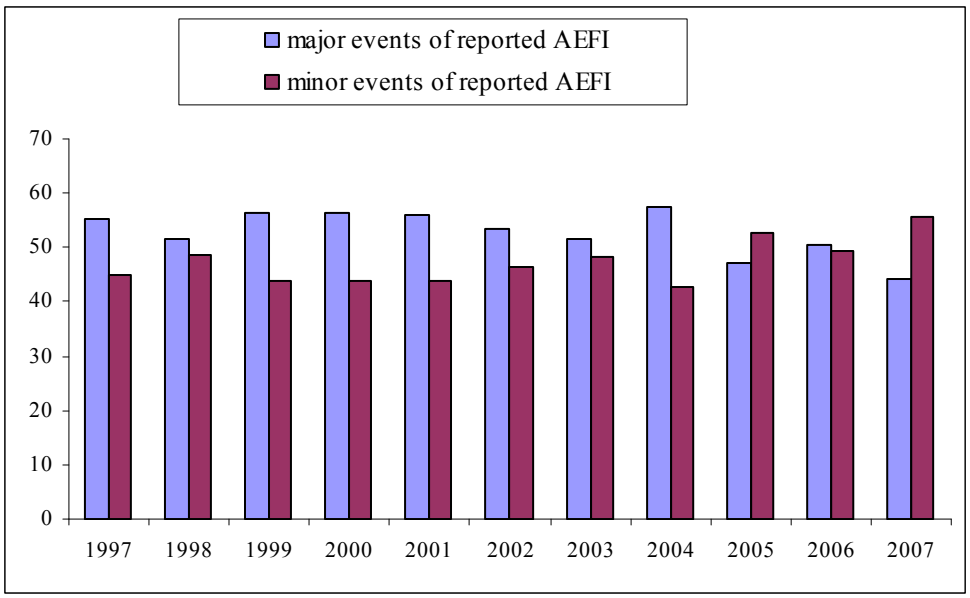

Figure 6. Percentage of reported minor and major AEFI in 1997-2007

The level of medical intervention may also illustrate the impact of adverse events. In 17.1% (170) of reports no medical help was sought or was not reported or recorded by us (range 16-21% for 2002-2006). Parents administered paracetamol suppositories, diazepam by rectiole or other home medication 132 times (13%; range 13-27% for 2002-2006). In Table 9 and Figure 7 intervention is shown according to highest level. In 68%, parents contacted the clinic or GP, called the ambulance or went to hospital. For the five previous years these percentages varied from 57-69%. Hospitalisation was necessary in 10% of the cases (range 8%-13% for 2002-2006).

Table 9. Intervention and events of reported AEFI in 2007 (irrespective of causality)

intervention⇒ / event⇓		?	none[a]	supp[b]	clinic[c]	gp tel[d]	gp visit[e]	ambu lance[f]	out-patient	emerg ency	hospital stay	other[g]	post mortem	total
local reaction		3	15	8	22	6	32	-	6	-	1	-	-	93
general illness	minor	15	54	73	36	33	117	-	26	6	21	9	-	390
	major	-	3	7	1	4	23	-	6	4	25	-	-	73
persistent screaming		3	9	16	5	4	3	-	-	1	-	1	-	42
skin symptoms		2	23	8	14	6	34	-	8	4	1	1	-	101
discoloured legs		-	14	14	16	9	19	-	4	2	3	-	-	81
faints		-	22	4	47	11	23	3	7	5	18	1	-	141
fits		2	5	2	-	2	13	5	6	7	27	-	-	69
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		-	-	-	-	-	-	-	-	-	1	-	-	1
death		-	-	-	-	-	-	-	-	-	3	-	1	4
total 2007		25	145	132	141	75	264	8	63	29	100	12	1	995

[a] homeopathic or herb remedies, baby massage or lemon socks are included in this group, as is cool sponging
[b] paracetamol suppositories, stesolid rectioles and other prescribed or over the counter drugs are included
[c] telephone call or special visit to the clinic
[d] consultation of general practitioner by telephone
[e] examination by general practitioner
[f] ambulance call and home visit without subsequent transport to hospital
[g] mainly homeopaths

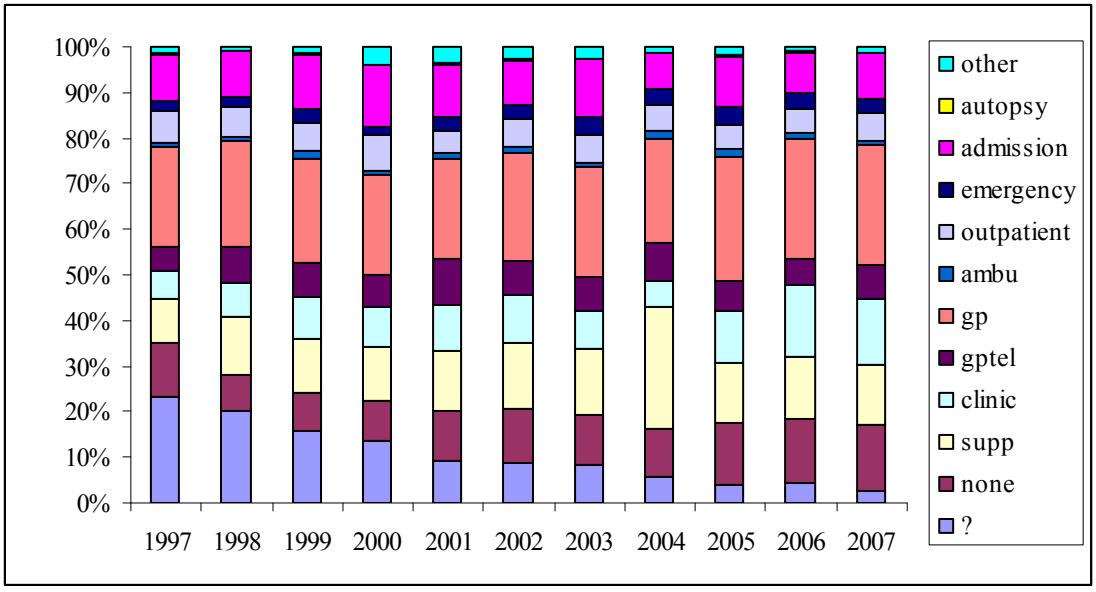

Figure 7. Highest level of medical intervention for AEFI 1997-2007

4.6 Causal relation

Events with (likelihood of) causality assessed as certain, probable or possible are considered adverse reactions (AR). In 2007, 72% of reports were adverse reactions, with exclusion of five non-classifiable events. Range for 2002-2006 is 73%-83%. Causality for major events is higher than for minor events, due to the inclusion of acknowledged side effects like collapse, discoloured legs and persistent screaming (Figure 8).

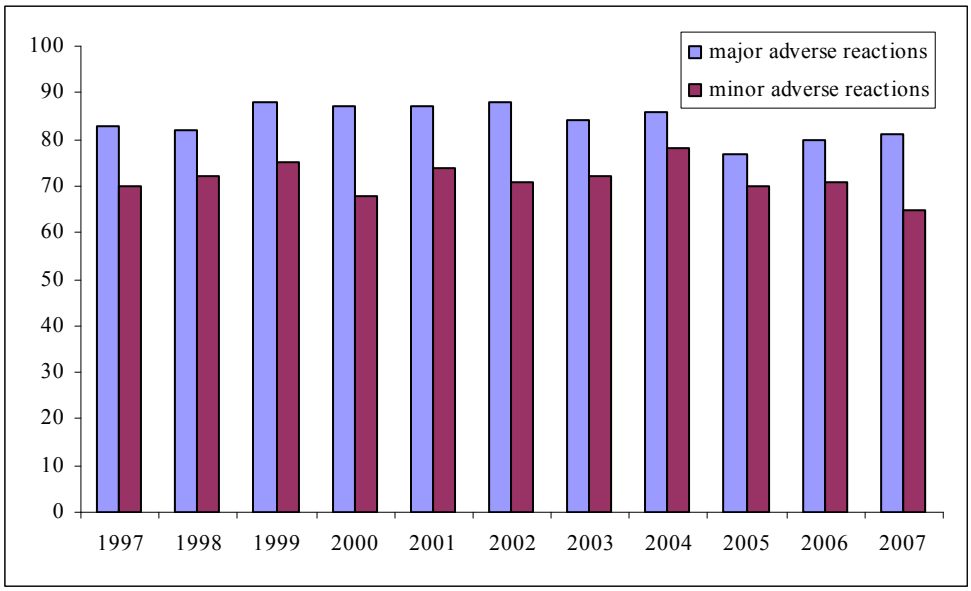

Figure 8: percentage minor and major AEFI with positive causality for 1997-2007.

There are great differences in causality between the different event categories (Table 10), but over the years very consistent. See for description and more detail the specific sections under 4.9 and discussion in chapter 5.

Table 10. Causality and events of reported AEFI in 2007 (% adverse reaction)

event ⇓ causality⇒	certain-probable-possible	improbable	non classifiable	total	(% AR*)
local reaction	92	1	-	93	(99)
general illness minor	233	154	2	390	(60)
major	39	32	2	73	(55)
persistent screaming	41	1	-	42	(98)
skin symptoms	61	39	1	101	(61)
discoloured legs	77	4	-	81	(95)
faints	124	17	-	141	(88)
fits	43	26	-	69	(62)
anaphylactic shock	-	-	-	-	-
encephalopathy/-itis	-	1	-	1	(0)
death	-	4	-	4	(0)
total 2007	710	280	5	995	(72)

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

Positive causality per dose varies between 60% for MMR and MenC vaccinations at fourteen months of age and 78% for the first dose of DTP-IPV-Hib and PCV7 at two months (Figure 9).

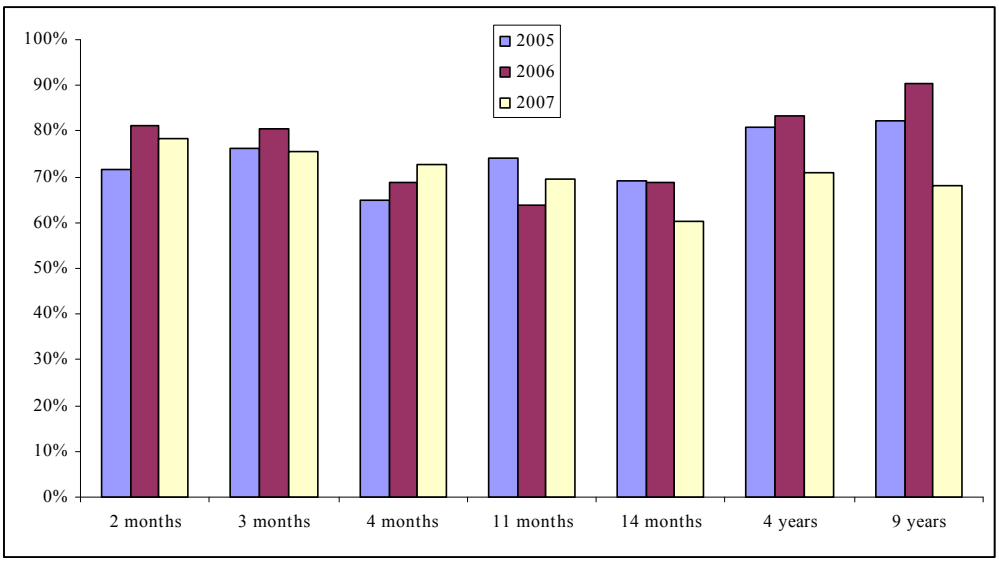

Figure 9: Percentage of reports with assessed causality per dose for 2007

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 2007 the expert panel has focussed on 37 cases.

Table 11: numbers of reports reassessed by the expert panel

event ⇓		expert panel	total	(% *)
local reaction		1	93	(1)
general illness	minor	4	390	(1)
	major	17	73	(23)
persistent screaming		-	42	-
skin symptoms		1	101	(1)
discoloured legs		-	81	-
faints		2	141	(1)
fits		7	69	(10)
anaphylactic shock		-	-	
encephalopathy/-itis		1	1	(100)
death		4	4	(100)
total 2007		37	995	(4)

* = % reassessments

The expert panel agreed with the causality assessment of the reports, 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. Some disease groups remain “empty” because no events were reported in 2007. The relative frequency of the different event categories has changed a little 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%. The share of faints and discoloured legs decreased compared to 2006.

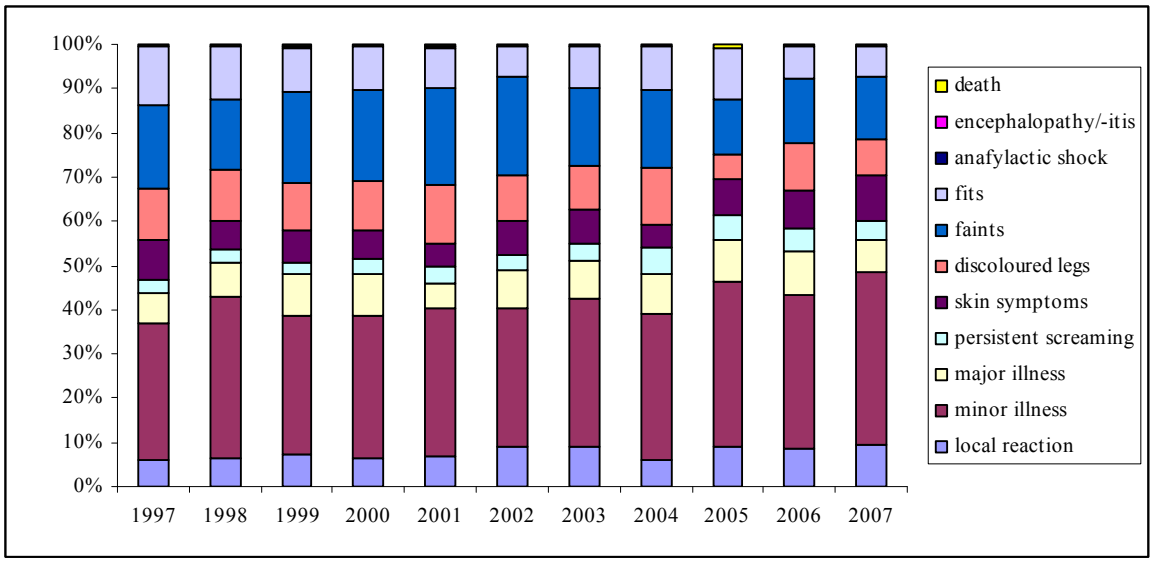

Figure 10: Relative frequencies of categories in reported AEFI 1997-2007

4.8.1 Local reactions

In 2007, 93 predominantly local reactions were reported, mostly following the fourth dose of DTP-IPV-Hib and PCV7 and the booster DTP-IPV at four years of age. Over the last three years reporting rates per dose fluctuate. Only for the first dose of DTP-IPV-Hib and PCV7 and the booster DTP-IPV at four years this change is significant (Figure 11). However, absolute numbers per dose are small and therefore 95% confidence intervals are large.

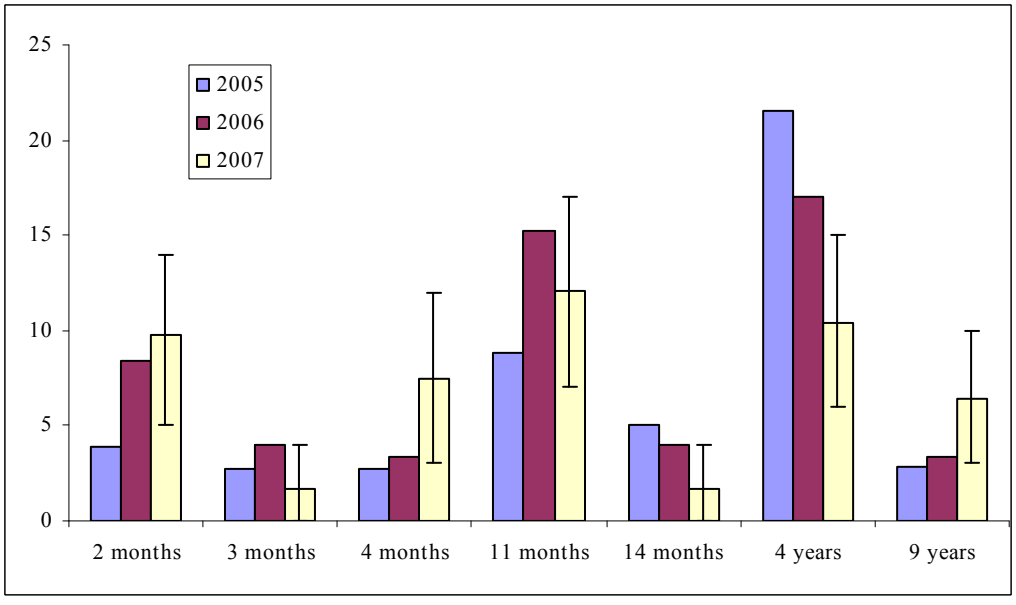

Figure 11: Reporting rate of local reactions per dose per 100,000 vaccinated children for 2005-2007

The majority of reported local events (63; 68%) were classified as minor reactions. 30 Reports (32%) were considered major local events because of size, severity, intensity or duration. Common

inflammation was the most prevalent aspect in 65 reports (25 considered major). 11 Reports concerned atypical local reactions with local rash or discoloration, possible infection, (de)pigmentation, haematoma, fibrosis, swelling, itch or pain, atypical time interval or combination of atypical symptoms. Three 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 12. Local events of reported AEFI in 2002-2007 (with major events and number of adverse reaction)

event	2002 (major)	2003 (major)	2004 (major)	2005 (major)	2006 (major)	2007 (major)	AR*
moderate/ pronounced	54 (8)	75 (13)	60 (10)	55 (7)	78 (20)	65 (25)	65
absces	8 (8)	6 (6)	14 (14)	13 (13)	6 (6)	5 (5)	5
pustule	1 (1)	-	1 (0)	1 (0)	-	-	-
atypical reaction	31 (3)	24 (2)	29 (0)	18 (0)	14 (2)	11 (0)	10
haematoma	2 (1)	2 (0)	2 (0)	-	-	1 (0)	1
nodule	17 (1)	4 (0)	6 (0)	4 (0)	1 (0)	5 (0)	5
avoidance	7 (0)	12 (2)	17 (1)	2 (0)	3 (0)	3 (0)	3
total 2007 (major event)	120 (22)	123 (23)	129 (25)	93 (20)	102 (28)	93 (30)	92

* number of adverse reactions

As expected, 99% of reported local events were considered causally related with the vaccination. The lowest percentage for causality in 2002-2006 was 98%. The percentage of reports with assessed causality per dose approaches 100% for all doses.

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 390 children the event was considered to be minor illness. Of the reported events 64% concerned the scheduled DTP-IPV-Hib vaccinations. In 2006 and 2005 this was 67% and 60%, respectively. In the last four years of whole cell DTP-IPV-Hib this ranged between 75 and 81%.

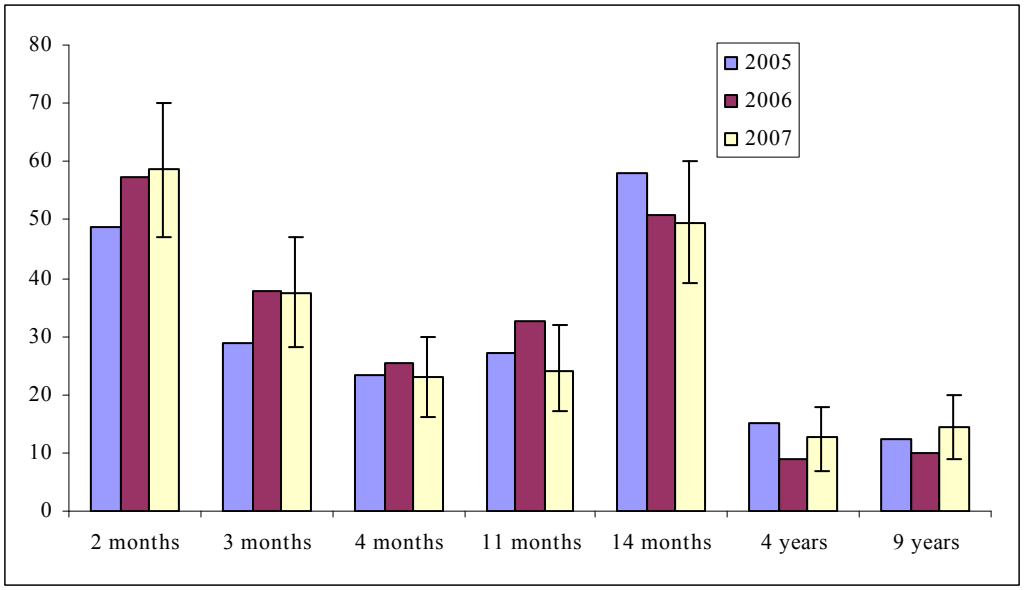

Figure 12: Reporting rate of minor general illness per dose per 100,000 vaccinated children for 2005-2007

As shown in Figure 12 there is some fluctuation in the reporting rate for this category per dose for the last three years, but there is no significant change.
Only very few times a definite diagnosis was possible; mostly working diagnoses were used. Fever is the most prominent symptom in 128 reports, 110 times considered possibly causally related. Crying was the main feature in 56 reports, predominantly following the first two vaccinations. Since the introduction of acellular pertussis vaccine for infants, pallor and/or cyanosis (11) and chills/myoclonics (14) are less frequently reported.
For the other working diagnoses numbers remained more or less the same over the last years (Table 13).

Table 13. Main (working) diagnosis or symptom in category of minor illness of reported AEFI in 2002-2007 (with number of adverse reactions)

Symptom or diagnosis	2002	2003	2004	2005	2006	2007	AR*
fever	70	100	212	120	135	128	110
crying	51	59	157	57	61	56	48
pallor and/or cyanosis	79	89	83	20	16	11	9
myoclonics and chills	28	39	46	7	9	14	11
prolonged/deep sleep/sleeping problems	9	10	10	7	14	10	10
rash(illness)/petechien	21	37	34	38	52	33	2
vaccinitis	20	31	31	39	24	23	23
airway and lung disorders	25	22	28	22	21	36	5
gastro-intestinal tract disorders	34	22	28	17	39	31	2
arthralgia/arthritis/coxitix/limping/disbalance/pain in limbs	6	8	6	18	5	3	1
behavioural problems/-illness	19	6	12	1	5	7	2
other	55	37	57	43	22	38	20
	417	460	704	389	403	390	233

* number of adverse reaction

In this category 40% of the reports (157) were considered to have improbable causal relation with the vaccination. For 2002-2006 this range was 27-34%. The percentage of adverse reactions decreased since the introduction of acellular DTP-IPV-Hib (Table 13 and Figure 13).

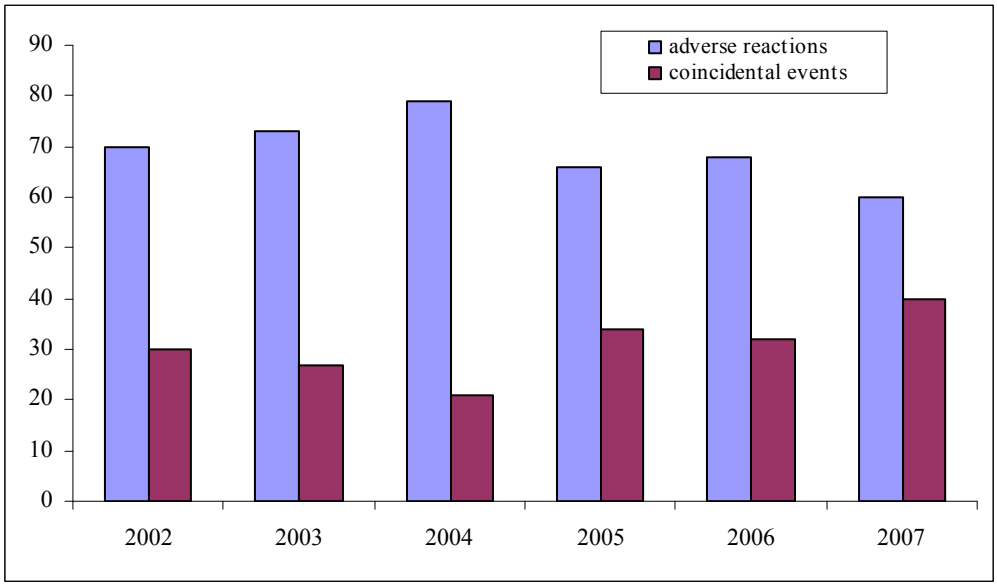

Figure 13: percentage of adverse reactions and coincidental reports in minor general illness for 2002-2007

For 2007 the percentage of adverse reactions varies between 41% for the booster DTP-IPV vaccination at four years of age and 69% for the second dose of DTP-IPV-Hib and PCV7, scheduled at three months (Figure 14). Over the years there is some fluctuation in these percentages. Only the decrease at nine years of age is significant compared to both 2005 and 2006.

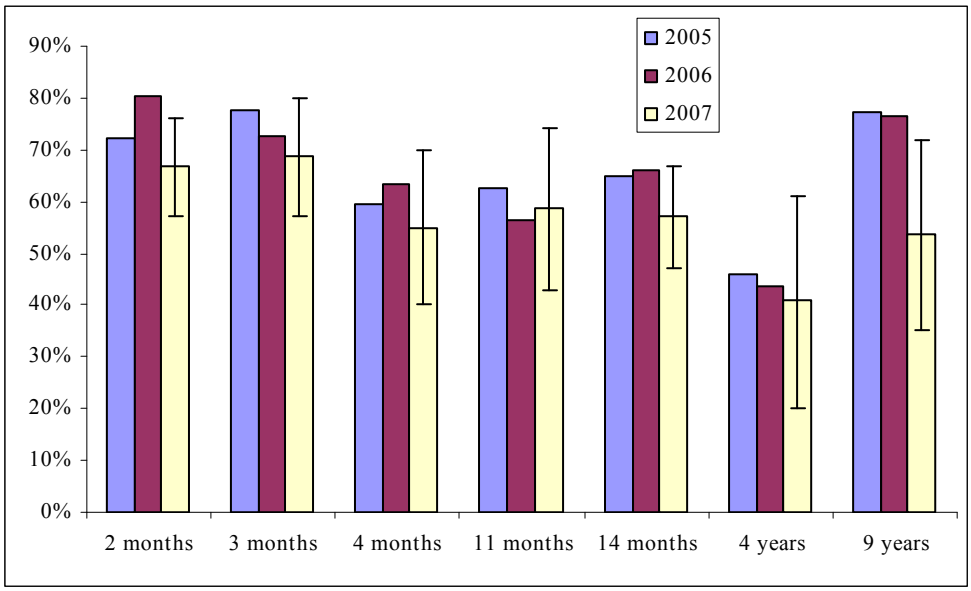

Figure 14: Percentage of reports on minor general illness with assessed causality per dose for 2007

4.8.3 Major general illness

Major general illness was recorded 73 times, a decrease compared with previous years, most prominent shown in a lower reporting rate following the first and fourth dose of DTP-IPV-Hib and PCV7 vaccination and the MMR and MenC vaccination, as shown in Figure 15. Only the change at 14 months is significant compared to both 2005 and 2006.

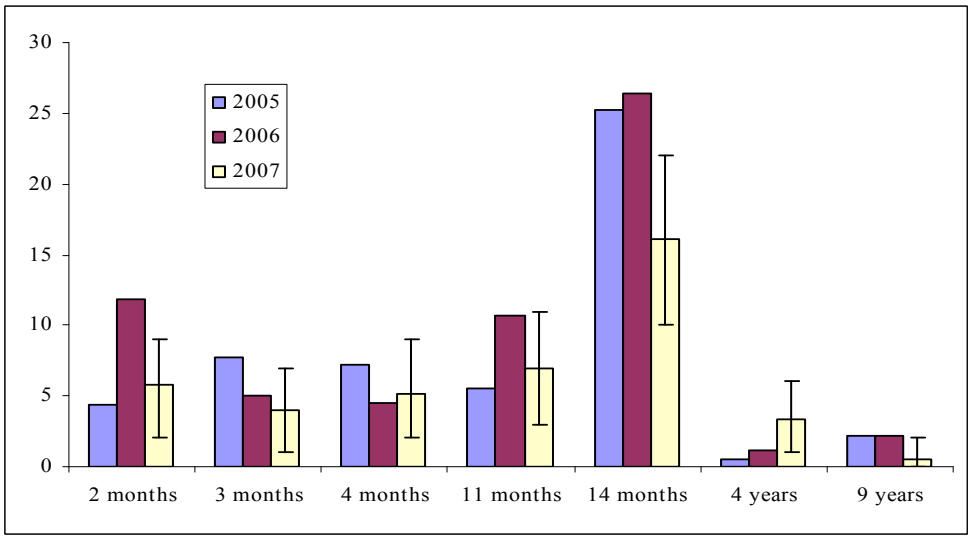

Figure 15: Reporting rate of major general illness per dose per 100,000 vaccinated children for 2005-2007

Very high fever (≥ 40.5 °C) was the working diagnosis in 41 cases, compared to 37-123 in 2002-2006. In 83% of these cases the fever was considered causally related to the vaccination (Table 14).

Table 14. (Working) diagnosis in category of major illness of reported AEFI in 2002-2007 (with number of adverse reactions)

symptom or diagnosis	2002	2003	2004	2005	2006	2007	AR*
very high fever (≥ 40.5 °C)	59	52	123	37	53	41	34
chills/myoclonics, accompanied with very high fever	2	3	5	1	2	-	-
gastro-intestinal tract disorder	4	2	7	2	4	1	0
respiratory tract disorder, apneu, respiratory insufficience	6	4	6	7	11	6	0
meningitis	4	3	3	5	4	7	0
vaccinitis/rash illness, accompanied with very high fever	7	5	6	13	17	2	2
infection	3	1	-	-	2	2	0
arthritis/osteomyelitis/JIA/myopathie	2	9	4	4	1	2	0
cardiomyopathy/myocarditis/arrhythmia	-	-	1	1	2	-	-
ITP	10	26	15	7	1	4	3
cerebellar ataxia	1	1	-	-	1	-	-
diabetes mellitus	1	4	2	1	1	-	-
kawasaki	-	-	2	2	-	1	0
guillain barre/plexus neuritis	-	-	2	-	-	-	-
optic neuritis/atrophy/visus disorder	-	2	-	-	1	-	-
intussusception	-	-	2	-	-	-	-
facial paralysis	-	-	-	2	-	-	-
urogenital tract disorder/henoch schonlein	1	1	5	1	-	1	0
ahoi	-	-	-	-	-	1	0
retardation/autism/pervasive-behavioral disorder	3	-	5	7	2	3	0
lymphadenitis colli/abcess	-	2	-	1	3	-	-
ALTE	-	-	2	-	-	-	-
shaken baby syndrome	-	-	1	-	-	-	-
other	9	4	2	3	6	2	0
total	113	119	194	97	111	73	39

* number of adverse reaction

In this category 55% (39) of the reports were considered adverse reactions. Over the years there is some fluctuation in this percentage (Figure 15).

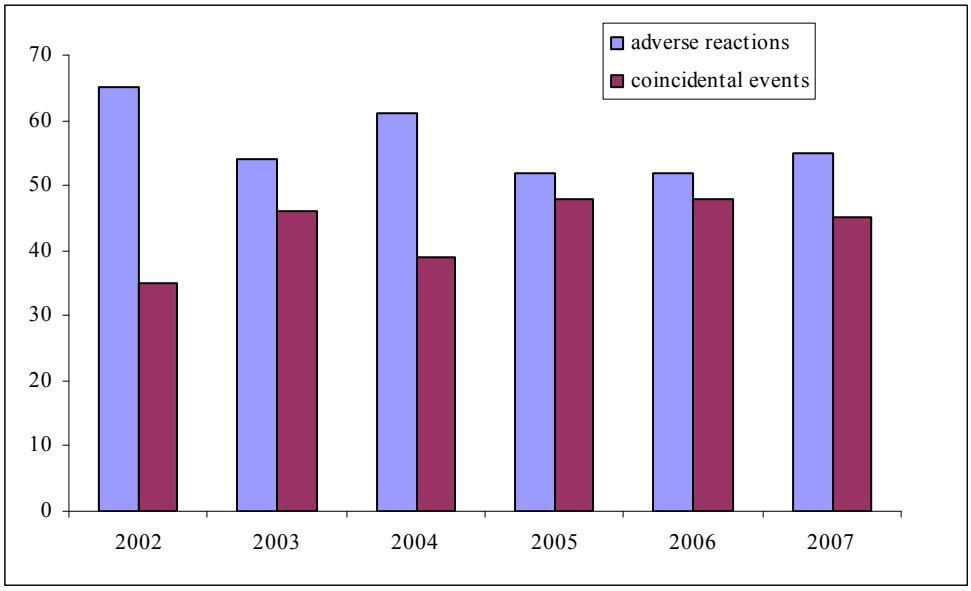

Figure 15: Percentage of adverse reactions and coincidental events in major general illness for 2002-2007

For 2007 the percentage of adverse reactions varies between 43% for the second dose of DTP-IPV-Hib and PCV7 vaccination at three months of age and 100% for the booster dose of DTP-IPV and MMR, scheduled at nine years. However, absolute numbers are small in this category, varying between one and 27 reports per dose for 2007 (Figure 16).

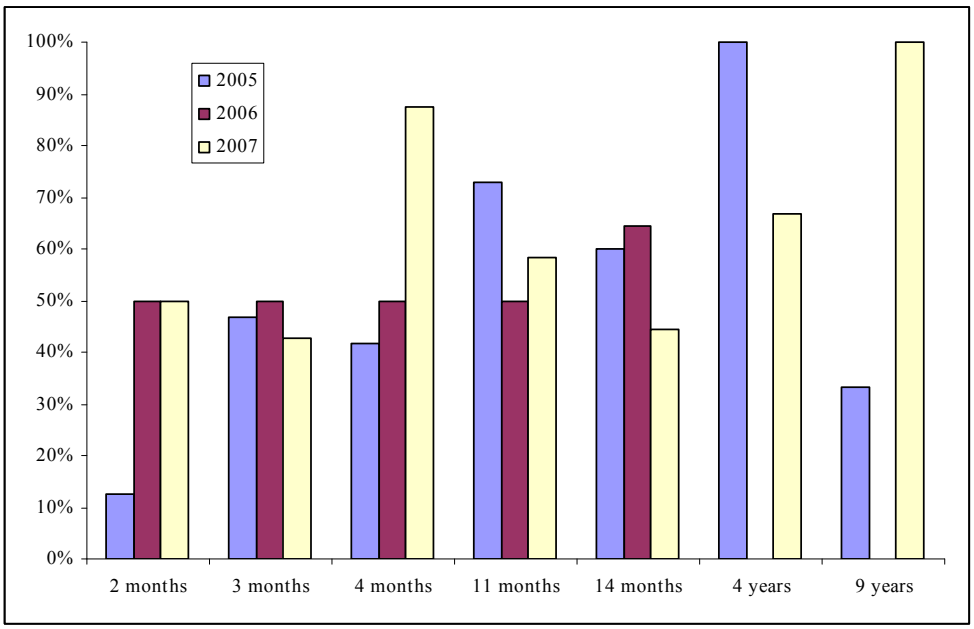

Figure 16: Percentage of adverse reactions in major general illness per dose for 2005-2007

4.8.4 Persistent screaming

In 2007 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 17).

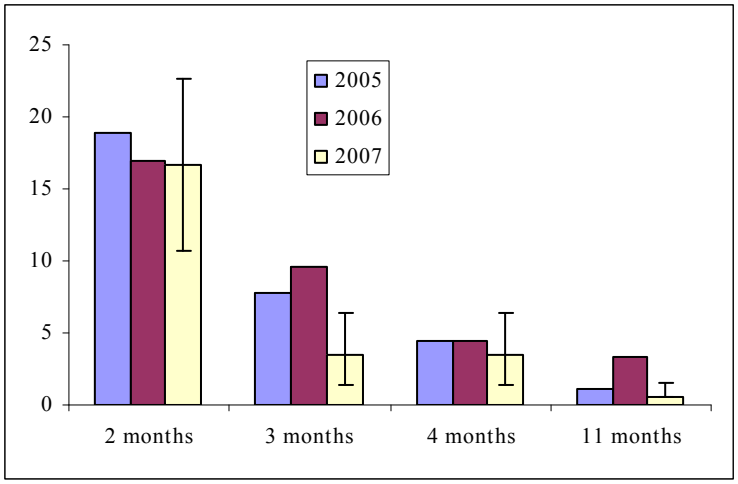

Figure 17: reporting rate of persistent screaming per dose per 100,000 vaccinated infants for 2005-2007

Additional symptoms were pain and swelling at the injection site, restlessness, pallor, myoclonic jerks and fever. 16 Parents gave suppositories, seven contacted the GP and one child was seen in the hospital (Table 10).
The overall causality for this category is high and constant over the last years, range 2002-2007 is 91-100% (Figure 18). The percentage of reports with assessed causality per dose approaches 100% for all doses.

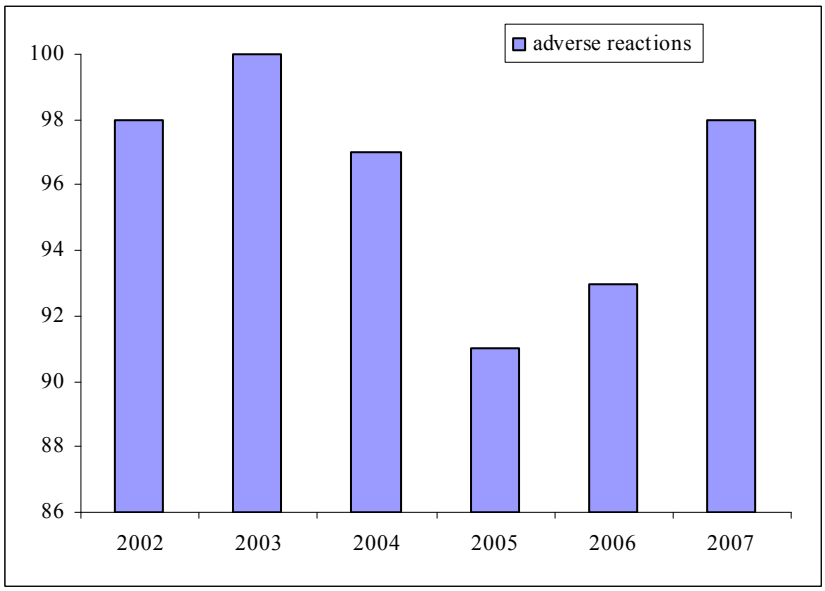

Figure 18: percentage of reports on persistent screaming with assessed causality for 2002-2007

4.8.5 General skin symptoms

In 2007, skin symptoms were the main or only feature in 101 reports, none of them classified as major. In 2002-2006 this ranged from 82-106. For the last three years the overall reporting rate is rather constant (Figure 19).

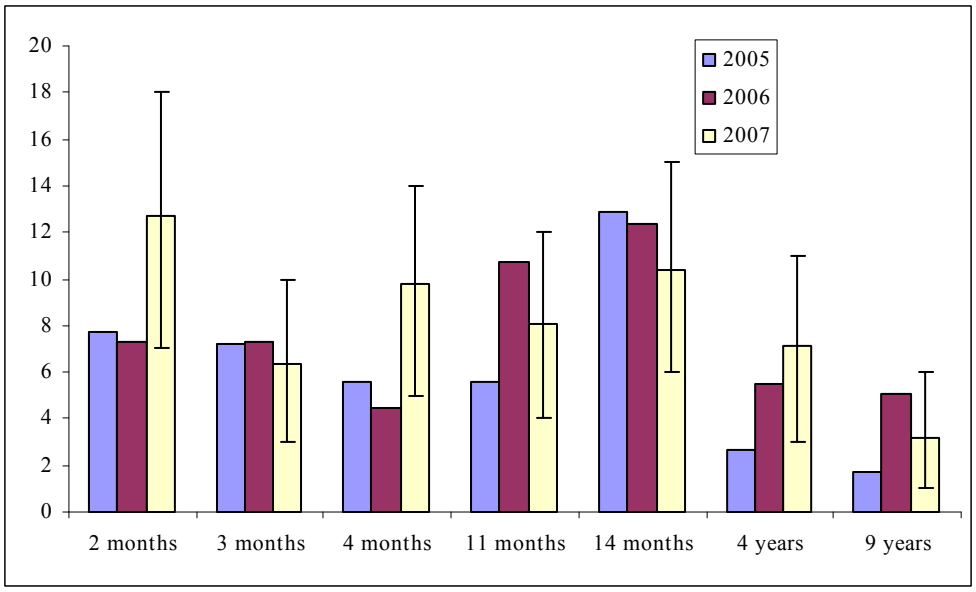

Figure 19: reporting rate of general skin symptoms per dose per 100,000 vaccinated children for 2005-2007

Exanthema, (increased) eczema and urticaria were the most frequent reported events (76%). Eleven times swelling/angiooedema were reported. Four reported children had petechial rash on upper body and/or face. Children with petechiae on the legs only are categorised under discoloured legs (Table 15).

Table 15. Diagnosis in category of general skin symptoms of reported AEFI in 2002-2007 with number of adverse reactions

diagnosis	2002	2003	2004	2005	2006	2007	AR*
angio-oedema/swelling	4	9	10	10	5	11	7
exanthema/erythema	61	58	60	46	52	55	32
urticaria	12	13	8	7	18	9	5
eczema (increase)	13	13	13	16	16	13	12
petechiae/purpura	7	4	5	2	3	4	2
other	7	7	10	1	3	9	3
total	104	104	106	82	97	101	61

Of the reports, 60% (61) were considered adverse reactions (range 2002-2006 is 37-62%, Figure 20).

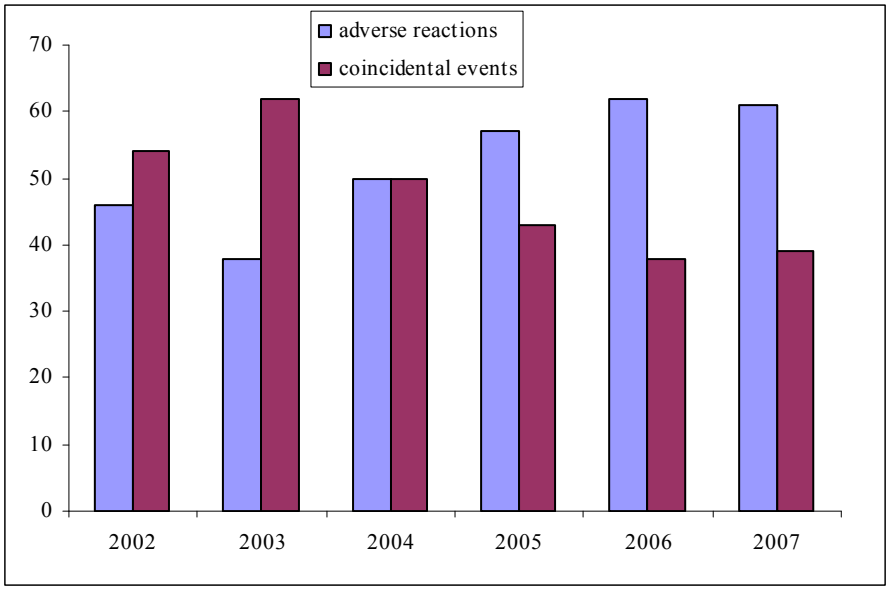

Figure 20: Percentage of adverse reactions and coincidental events in skin symptoms for 2002-2007

The causality per dose peaks at three months of age with 100% assessed causality and is lowest for nine year olds (17%). However, absolute numbers per dose are small (range 6-22) Figure 21.

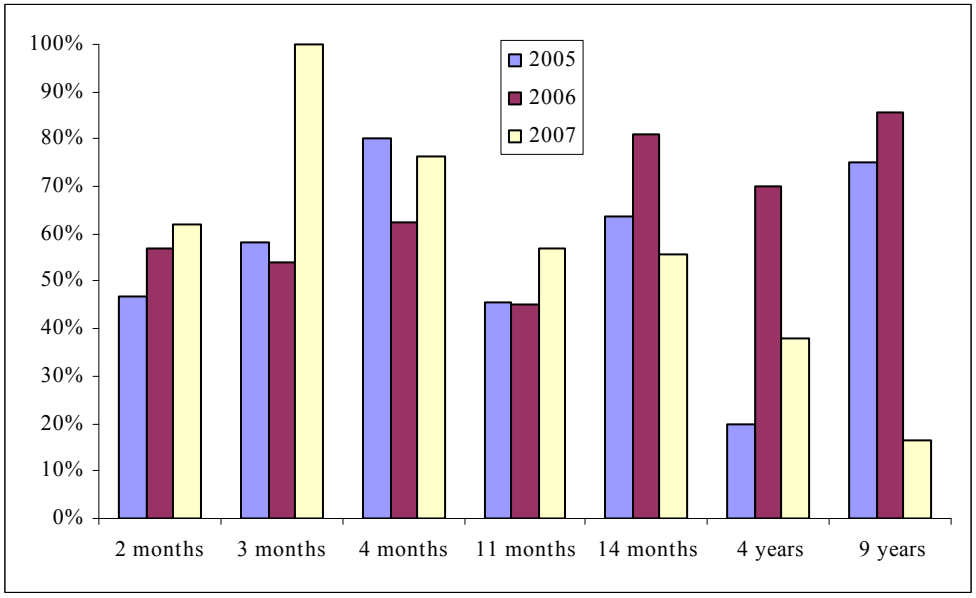

Figure 21: Percentage of reports on skin symptoms with assessed causality per dose for 2007

4.8.6 Discoloured legs

Starting from 1995, discoloured legs are listed in 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 and are also grouped in this category. The same applies for swollen limbs.

In 2007 we received 81 cases of discoloured legs, mostly reported after the first two doses of DTP-IPV-Hib. Last years the reporting rate fluctuates between 24 and 66 per 100,000 vaccinated infants under one year of age (Figure 22).

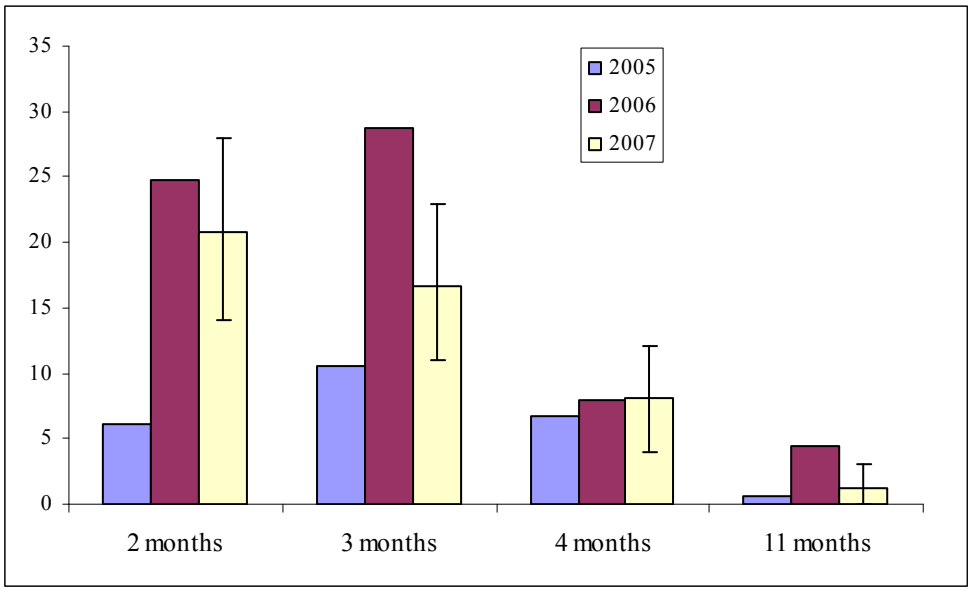

Figure 22: Reporting rate of discoloured legs per dose per 100,000 vaccinated infants for 2005-2007

Six reports were considered to be blue legs (twice double-sided), 46 red legs (22 double sided) and 12 (10 double sided) purple legs. In 11 cases leg petechiae without (noticed prior discoloration were reported (Table 16).

Table 16. Discoloured legs of reported AEFI in 2002-2007 with number of adverse reactions

diagnosis	2002	2003	2004	2005	2006	2007	AR*
blue legs	26	29	36	5	12	6	6
red legs	40	51	130	26	60	49	46
purple legs	43	24	69	8	30	12	11
petechiae only	23	26	40	15	19	11	11
swollen limb	5	4	4	3	3	1	1
total	137	134	279	57	124	81	77

* number of adverse reactions

Causal relation with the vaccines was inferred in all but four cases. In the last five years the rate of positive causality always was ≥ 95%. The same applies to the causality per dose.

4.8.7 Faints

In this event category, collapse (hypotonic-hyporesponsive episode, HHE), syncope (fainting) and breath holding spells (BHS) are listed (Table 17).

In 2007 collapse was reported in 96 cases. This is an increase compared with 2005 and 2006, but a sharp decrease in numbers compared with 2001-2004. In 75% of cases collapse occurred after the first DTP-IPV-Hib and PCV7 vaccination. In 2005 and 2006 this was 37% and 61%, respectively. In 2001-2004 this ranged from 60%-73%. Numbers diminished with dose number and age, similar to 2001-2004.[32] See for reporting rates per dose Figure 23.

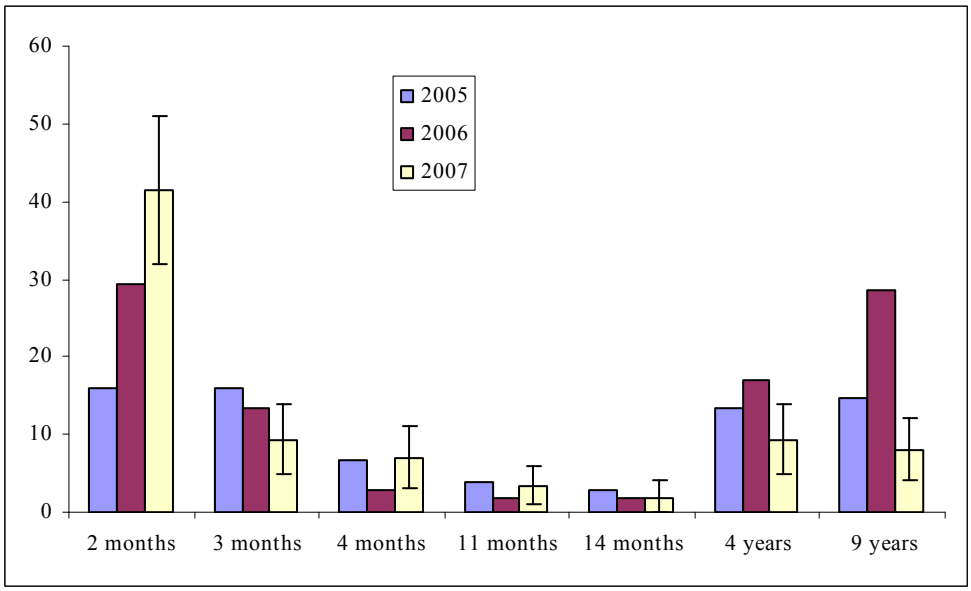

Figure 23: Reporting rate of faints per dose per 100,000 vaccinated children for 2005-2007

BHS occurred 14 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 31 times, a decrease compared to the two previous years.

Table 17. Diagnosis in category of faints of reported AEFI in 2002-2007 (with number of adverse reactions)

diagnosis	2002	2003	2004	2005	2006	2007	AR*
collapse	270	210	318	75	76	96	79
breath holding spell	8	9	23	6	11	14	14
fainting	19	25	37	52	82	31	31
total	297	244	378	133	169	141	124

* number of adverse reactions

Events in this category are acknowledged adverse reactions following vaccination. The percentage of causally related events varies between 84% and 97% in 2002-2007. For 2007 the percentage with assessed causality per dose varies between 69% for the second dose of DTP-IPV-Hib and PCV7 and 100% for doses at 14 months, four and nine years of age.

4.8.8 Fits

Epileptic seizures and (febrile) convulsions 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 (42 out of 45), occurring predominantly after the fourth DTP-IPV-Hib and PCV7 (9) and MMR1/MenC (30) vaccinations. For MMR this is a sharp decrease compared to 2006, for DTP-IPV-Hib and PVC7 this number is equal to 2006 (Figure 24).

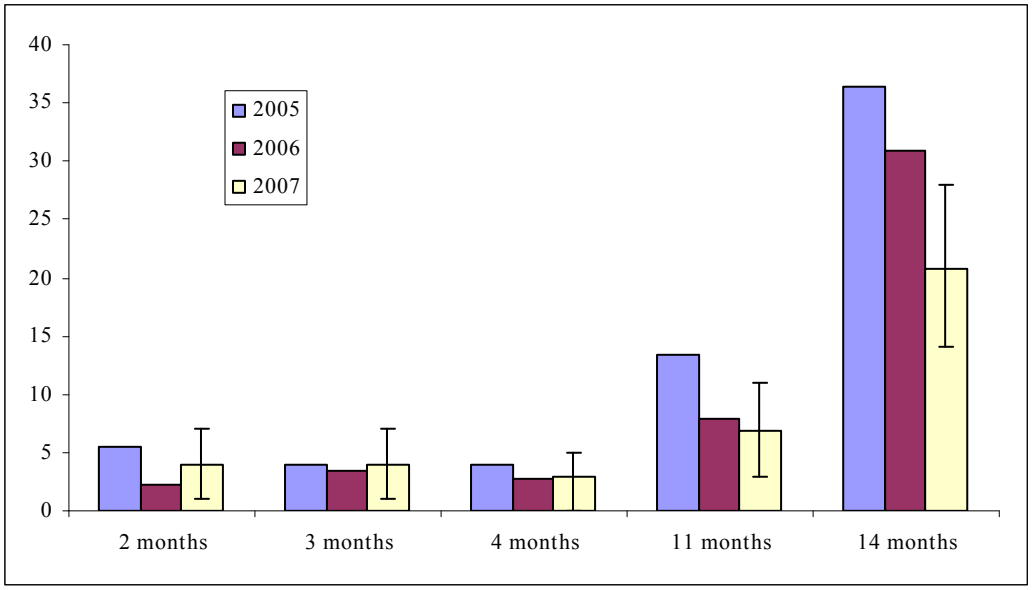

Figure 24: Reporting rate of fits per dose per 100,000 vaccinated children for 2005-2007

Three non-febrile convulsions were reported.
Six children with epilepsy were reported. In none of these children (fever caused by) the vaccine was regarded as trigger.
In 2007 atypical attacks were recorded 18 times, equal to the previous year and lower than 2002-2005. Six of these atypical attacks were accompanied by fever. None of these children fulfilled the case definitions for collapse or convulsion.

Table 18. Diagnosis in category of fits of reported AEFI in 2002-2007 (with number of adverse reactions)

diagnosis		2002	2003	2004	2005	2006	2007	AR*
febrile convulsion	simplex	22	28	45	34	30	25	18
	complex	20	23	32	24	24	13	11
	atypical	3	13	13	7	3	4	3
non febrile convulsion		-	6	8	6	6	3	1
epilepsy		5	5	9	4	3	6	0
atypical attack		41	57	104	43	19	18	10
total		91	132	211	118	85	69	43

* number of adverse reactions

Causality was assessed in 76% of the febrile convulsions (range 2002-2006 69%-90%). For atypical attacks this percentage was 56%, varying between 53% and 74% in the last six years (Figure 25).

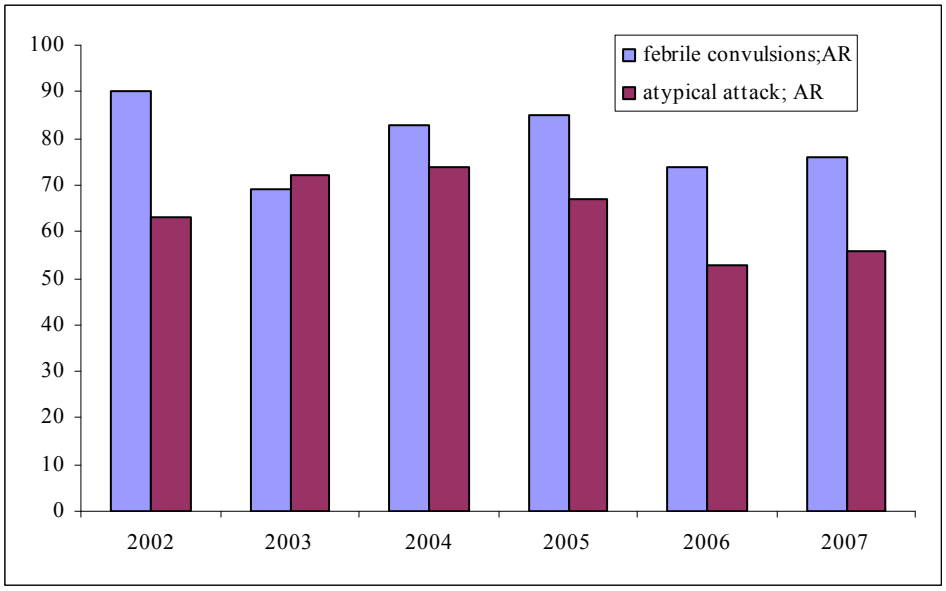

Figure 25: Percentage of febrile convulsions and atypical attacks with assessed causality for 2002-2007

The percentage of febrile convulsions with assessed causality for the booster DTP-IPV-Hib and PCV7 vaccination was 56%, compared to 81% for MMR and MenC at 14 months (Figure 26). For atypical attacks the percentages per dose ranged between 20% and 100%. However absolute numbers are small for this diagnosis.

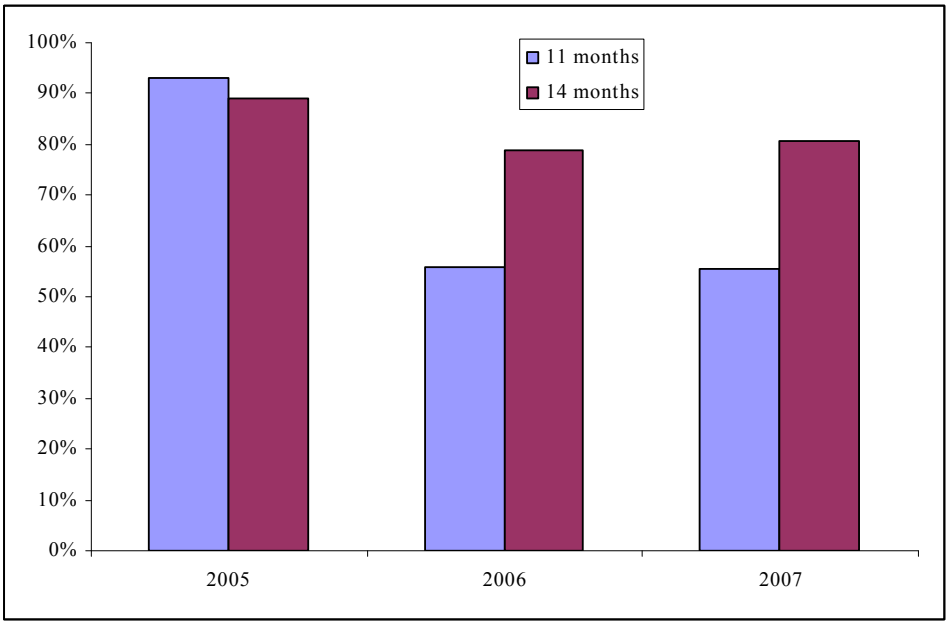

Figure 26: percentage of reports on febrile convulsions with assessed causality per dose for 2005-2007

4.8.9 Encephalopathy/encephalitis

The only event reported in 2007 listed in this category was considered a chance occurrence and not induced or aggravated by the vaccination (Table 19)

Table 19. Encephalopathy/encephalitis and vaccines of reported AEFI in 2007

child	sex	age[a]	vaccines	interval	symptoms/diagnosis	causality
A	F	11 months	dtp-ipv-hib 4 pcv7 4	3 days	Fever, encephalitis, positive culture in faeces for enterovirus	no

[a] age at vaccination

4.8.10 Anaphylactic shock

There were no reports on anaphylactic shock in 2007. 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 2007, four children were reported, who died following vaccination (Table 20). The reports concerned three boys and one girl. Autopsy was performed only once. Without full post-mortem investigation a definite diagnosis is often impossible. In all four cases death was judged not to be caused or hastened by the vaccination.

Table 20. Death and vaccines of reported AEFI in 2007

child	sex	age[a]	vaccines	time interval illness	time interval death	symptoms/diagnosis	causality	autopsy
A	m	7.5w	dtp-ipv-hib 1 pcv7 1	20 h	20 h	clinical SIDS	no	no
B	m	4m	dtp-ipv-hib 3 pcv7 3	1d	3w	apneu, bradycardy, asystoly, abnormal EEG, bronchopneumonia	no	yes
C	f	15m	dtp-ipv-2	before	4.5 m	epilepsy, encephalopathy,	no	no
D	m	4m	dtp-ipv-hib1+hepb1	<24h	<24h	crying, no fever, positive test RSV, clinical SIDS	no	no

[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 increases 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.[33,34,35] 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 2007.
In 2007 there have been no changes in the programme. Due to the introduction of seven valent conjugated pneumococcal vaccine in the programme since April first 2006, 2007 show results of a full year use of this vaccine. Furthermore, MMR was obtained from multiple manufacturers, with different formulation and presentation. This may influence the safety profile of this vaccine. 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 2007

5.1.1.1 Number of reports, vaccines and dose, adherence to the programme

Since 2005 number of reports fluctuates at a lower level, compared to the period of whole cell DTP-IPV-Hib vaccine. This is in line with expectation since acellular pertussis vaccines are known to have a more favourable safety profile both for common and severe events.[36,37,38] In 2007 the number of reports decreased with 14% compared to the previous year. In 2005 and 2006 the overall reporting rate was 5.7 and 6.4 per 1000 vaccinated children respectively, compared to 5.5 (95%CI 5.2-5.9). The 95% confidence interval of the overall reporting rate of 2007 does not contain the rate of 2006. However, these rates are based on birth cohort and vaccination coverage data of 2005. Compared with 2005 the birth cohort of 2007 has diminished with more than 7,000 infants (www.statline.nl). Assuming similar coverage and based on the actual birth cohort of 2007, the overall reporting rate comes up to 5.7 (95%CI 5.4-6.1). This is slightly lower than 2006 and in line with 2005. Therefore, the smaller birth cohort of 2007 partly explains the decrease in numbers in this year.
Seven valent conjugated pneumococcal vaccine (PCV7) was added to the RVP for all children born from April first 2006 onwards. Compared to 2006, the reporting rate for DTP-IPV-Hib, with or without PCV7, is equal, namely 4:1000 vaccinated infants. Therefore a full year use of PCV7 had no great influence on the number of reports. This is congruent with the results of a large questionnaire study on more rare, severe adverse events, conducted from 2003 until 2007. We found no differences in incidence rates for prolonged crying, high fever and pallor between DTaP-IPV-Hib and DTaP-IPV-Hib+PCV7.[39]
Comparing scheduled and actually administered vaccines a slight decrease in adherence to the programme of 2007 is seen at 11 month old infants, probably due to the fact that part of these children

is born before April 2006 and therefore are not eligible to receive PCV7. These children followed the programme of 2006.
Reports following MMR and MenC have decreased significantly, not explained by the decreasing birth cohort, as shown in Figure 5. In contrast to previous years, more than 90% of MMR came from different manufacturers. A difference in risk of convulsions and aseptic meningitis was seen when different vaccine virus strains are used, but overall, reactogenicity of the currently used MMR vaccines is comparable.[40,41,42] Therefore this change in used vaccine is probably no explanation for the decrease in reports following MMR.

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.[36,37,38] In 2007 the overall reporting rate for major events has decreased compared to 2005 and 2006. The absolute number of reported major adverse events was lowest for the past three years, but the rate of major adverse reactions was highest. This phenomenon is due to the larger decrease of major coincidental events compared to major events with assessed causality. The decrease is evenly distributed over the categories, except major local reactions.
The overall reporting rate for minor events is equal to 2006 and slightly higher than 2005. Therefore decrease in minor events is very small, but causality rate for minor events has decreased to 65% (range 2002-2006 70%-78%). This is mainly due to more coincidental reports categorised in minor general illness, whereas the reporting rate in this category remained the same compared to 2005 and 2006.

5.1.3 Specific events

The decrease in numbers is apparent in nearly all event categories, most prominent in those categories that contribute to major events. See for additional information the subsections below.

5.1.3.1 Local reactions

Related to the decreased birth cohort, the reporting rate for local reactions was nearly equal to the two previous years. However, the contribution of major events to this category has increased from 22% and 27% in 2005 and 2006, respectively, to 32% in 2007. As shown in Figure 10 the reporting rate is highest for the booster vaccinations of DTP-IPV(-Hib) at 11 months and 4 years of age. This increased risk of extensive local reactions is described in literature.[43,44,45] 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 will repeat this study in children, who received only acellular DTP-IPV-Hib as an infant.

5.1.3.2 Minor general illness

The overall reporting rate in this category does not differ significantly from 2006 and 2005, although there were some fluctuations in the rates per dose. The reports of acknowledged side effects like fever, crying, pallor/cyanosis and myoclonics are more or less the same since the introduction of acellular DTP-IPV-Hib. For fever and crying these numbers also correspond with the years before 2004. However, pallor and myoclonics are significantly less reported following acellular DTP-IPV-Hib compared to whole cell pertussis vaccine. The introduction of PVC7 to the programme had little effect on these numbers. 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 rates of the acellular vaccine was negligible.[39] 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 in the latter group.[46] 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.[47,48,49] Comparing these results is hampered by different schedules, vaccine combinations, methods and levels of assessment and lack of uniform case definitions. [37,38,50]

5.1.3.3 Major general illness; very high fever and vaccinitis

Both the absolute number and the overall reporting rate have decreased compared to 2005 and 2006. This is most prominent for numbers following the first and fourth DTP-IPV-Hib and PCV7 dose and the administration of MMR and MenC at 14 months of age. Especially the reports of very high fever (≥ 40.5 °C) and vaccinitis/rash illness, accompanied by very high fever, following MMR have decreased.

59% of the cases with very high fever were reported following DTP-IPV-Hib and PCV7, compared to 62% in 2006 and 59% in 2005. However, there is less emphasis on the one-year-olds in the last two years; of these cases 29% were reported following the fourth dose compared to 35% and 74% in 2006 and 2005, respectively.

In the literature difference in fever height intensity 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.[46,47,48,49] The questionnaire study on more severe adverse reactions, mentioned earlier, found no statistically significant difference for the two groups.[39]

Vaccinitis is defined as rash and fever potentially 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). The number of cases in minor general illness is equal to 2006, but vaccinitis categorised in major general illness has decreased from 15 in 2006 to two in the current year. We already discussed the shift to MMR from different manufacturers and believe this temporary change had little effect on these numbers.[42]

5.1.3.4 Persistent screaming

The number of reports of persistent screaming is rather stable, except for 2004, which was marked by a tremendous increase, due to adverse publicity.[26] There has always been a known underreporting of persistent screaming in the passive surveillance. Incidence rates are difficult to compare, because of different case definitions, but vary from 1-10 per 1000 children. For the last three years the reporting rate of this event following the first DTP-IPV-Hib and PCV7 vaccination varies between 0.19 and 0.17 per 1,000 infants (95%CI of 2007 0.11-0.23; Figure 17). In the questionnaire study we found inconsolable crying for three hours and more following the first dose of DTP-IPV-Hib, with or without co-administered PCV7, in 4 per 1,000 infants.[39]

5.1.3.5 Discolored legs

The number of reports in this category has fluctuated during the last three 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). However, in the current year all children received PCV7 and reports decreased by 35% of these cases. Ongoing surveillance is necessary to gather more accurate numbers on this subject.

5.1.3.6 Faints; collapse

In the category "Faints" the number of reports decreased, due to fewer reports on fainting in older children. There has always been fluctuation in reports on fainting, caused by known underreporting. On the contrary, number of reports on collapse increased with 26%, despite the smaller birth cohort. 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.[36,37,38] 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. In the current year again an increase is seen, perhaps caused by a full year use of PCV7. 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.[39,51] Therefore reduced underreporting is probably a less significant factor in the explanation of this increase.

5.1.3.7 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 better safety profile compared to whole cell vaccines.[36,37,38] The introduction of PCV7 had no great influence on the reporting rate at these age groups, as shown in Figure 24.
In the year under report the decrease is most obvious following MMR and MenC vaccination. As discussed in section 5.1 and 5.3.3, the use of MMR from different manufacturers is probably no explanation for this decrease.[40,41,42]

5.1.3.8 Death

This year four 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 the children. Neither, indirect causality was considered due to delay in treatment or aggravation of symptoms because of the vaccination. 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 time related to a vaccination will prevent rumours surfacing, even if on first sight causal relation seems to be remote.

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.[13,14,52,53,54] 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.[55] 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 namebased reports facilitate follow up and some other systematic studies, like nested case-control studies.[56] 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.[57,58,59,60] Of course, after vaccination does not mean caused by vaccination. The RIVM requests an expert panel to reassess selected cases with complete agreement on diagnosis and causality. Some other countries, like Canada, USA and Australia have followed suit.[61,62,63] 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.[64] 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.[65]

5.2.3 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. 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 adverse events, especially auto-immune disorders.[66] 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. In the light of the possible introduction of HPV in 2009, we are preparing a monitoring plan in which we deal with all aspects, mentioned above.

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] The year under report shows results of a full year use of PVC7. Despite this fact, a decrease of reported events occurred. Our questionnaire study shows little impact on incidence rates of DTP-IPV-Hib and concurrently administered PCV7.[39] The smaller birth cohort partly explains the decrease in numbers for the year under report. Although there were no changes in the programme, for MMR there was shifting to products of different manufacturers. Frequent shifting hampers more precise description of the safety profile of vaccines /vaccine combinations. However, currently used MMR vaccines from different manufacturers show no great differences in safety profile.[42]
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.[66,67,68,69] 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 2008;
- 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 995 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: Resume Product Information

Vaccines in RVP	Producer	constituents	
DTP-IPV-Hib vaccine	Aventis Pasteur	Diphtheria toxoid	≥ 30 IE
Diphtheria, acellular		Tetanus toxoid	≥ 40 IE
Pertussis, Tetanus and		Pertussis toxoid (PT)	20 µg
inactivated Poliomyelitis		Filamenteuze hemagglutinine (FHA)	20 µg
vaccine mixed with		Fimbriae agglutinogenen 2 and 3 (FIM)	5 µg
conjugated Hib-vaccine		Pertactin (PRN)	3 µg
	RVG	Inactivated poliovirus type 1 (Mahoney)	40 DE
0.5 ml	32118	Inactivated poliovirus type 2 (MEF-1)	8 DE
		Inactivated poliovirus type 3 (Saukett)	32 DE
		Haemophilus influenzae type b polysaccharide	10 µg
		Conjugated to tetanus toxoid (PRP-T)	20 µg
DTP-IPV-Hib-HepB vaccine	GSK	Diphtheria toxoid*	≥ 30 IE
Diphtheria, acellular		Tetanus toxoid*	≥ 40 IE
Pertussis, Tetanus,		Pertussis toxoid* (PT)	25 µg
inactivated Poliomyelitis and		Filamenteuze hemagglutinine* (FHA)	25 µg
Hepatitis B vaccine mixed		Pertactin* (PRN)	8 µg
with conjugated Hib-vaccine		Hepatitis-B**,***	10 µg
		Inactivated poliovirus type 1 (Mahoney)	40 DE
0.5 ml	EU/1/00/152/001	Inactivated poliovirus type 2 (MEF-1)	8 DE
	EU/1/00/152/002	Inactivated poliovirus type 3 (Saukett)	32 DE
	EU/1/00/152/003	Haemophilus influenzae type b polysaccharide***	10 µg
	EU/1/00/152/004	Conjugated to tetanus toxoid (PRP-T)	20-40 µg
	EU/1/00/152/005	*adsorbed to aluminiumhydroxide	0.95 mg
	EU/1/00/152/006	**produced in yeast (Saccharomyces cerevisiae)	
	EU/1/00/152/007	by recombinant DNA techniques	
	EU/1/00/152/008	***adsorbed to aluminium phosphate	1.45 mg
DTP-IPV vaccine	Sanofi Pasteur	Diphtheria toxoid	≥ 2 IE
Diphtheria, Acellular		Tetanus toxoid	≥ 20 IE
Pertussis, Tetanus and		Pertussis toxoid (PT)	2.5 µg
inactivated Poliomyelitis		Filamentous hemagglutinin (FHA)	5 µg
vaccine		Fimbriae 2 and 3 (FIM)	5 µg
		Pertactin (PRN)	3 µg
0.5 ml	RVG	Inactivated poliovirus type 1	40 DE
	27569	Inactivated poliovirus type 2	8 DE
		Inactivated poliovirus type 3	32 DE
		adsorbed to aluminium phosphate	0.33 mg Al
DT-IPV vaccine	NVI	Diphtheria toxoid *	≥ 5 IE
Diphtheria, Tetanus and		Tetanus toxoid*	≥ 20 IE

inactivated Poliomyelitis vaccine 1 ml	 RVG 17641	Inactivated poliovirus type 1 Inactivated poliovirus type 2 Inactivated poliovirus type 3 *adsorbed to aluminium phosphate	≥ 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	NVI RVG 17654	Mumps virus Measles virus Rubella virus	≥ 5000 p.f.u. ≥ 1000 p.f.u. ≥ 1000 p.f.u.
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	Aventis Pasteur MSD SND EU/1/01/183/001 EU/1/01/183/018	Hepatitis B-virus surface antigen, recombinant* (HBsAg) Adsorbed to amorphe aluminiumhydroxy-phosphatesulphate *yeast strain Saccharomyces cerevisiae (2150-2-3)	5 μg 0.25 mg

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