RIVM report 240071004/2007

Adverse Events Following Immunisation under the National Vaccination Programme of the Netherlands
Number XIII - Reports in 2006

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This investigation has been performed by order and for the account of the Ministry of Health, Welfare and Sport and the Inspectorate of Health Care, within the framework of project V/240071/01/BW, Safety Surveillance of the National Vaccination Programme.

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Het rapport in het kort

Postvaccinale gebeurtenissen binnen het Rijksvaccinatieprogramma.
Deel XIII- Meldingen in 2006

De bijwerkingenbewaking van het Rijksvaccinatieprogramma over 2006 liet een duidelijke toename zien van het aantal meldingen. Dit betrof vooral stijging van meldingen na DKTP-Hibvaccinaties. De toename in het aantal meldingen is mogelijk veroorzaakt door de geleidelijke overgang naar een DKTP-Hibvaccin met vijf kinkhoestcomponenten. Deels is de stijging ook toe te schrijven aan vermindering van de onderrapportage na invoering van het acellulaire combinatievaccin in januari 2005. De toevoeging van pneumokokkenvaccin vanaf 1 april 2006 heeft weinig invloed gehad op de stijging. In 2006 zijn in totaal 1159 meldingen ontvangen. Hiervan werd 76% als bijwerking van de vaccinaties beschouwd. De rest (24%) 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 1159 meldingen betrof het in 875 (76%) gevallen een bijwerking. Hierbij ging het in 51% 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. Er is één kind met hersenontsteking gemeld in 2006; dit berustte niet op de vaccinatie maar op een andere oorzaak. 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 zes 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 voorbijgaand 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

Abstract

Adverse Events Following Immunisation under the National Vaccination Programme of the Netherlands
Number XIII- Reports in 2006

Adverse events following immunisation (AEFI) in the National Vaccination Programme of the Netherlands (RVP) have been monitored through an enhanced passive surveillance system by 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 2006 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 1159 AEFI were reported. Of these, 2 were unclassifiable because of insufficient information. In 76% (875) of the classifiable events a possible causal relation with vaccination was established. These concerned major adverse reactions in 51% and minor adverse reactions in 49% of the reports. Of the reported adverse events 24% (282) were considered chance occurrences. Compared to 2005 there was an increase in number of reports, probably due to reduced underreporting. Perhaps the phased introduction of a DTP-IPV-Hib vaccine with five pertussis components was of some importance. The uptake of Pneumococcal vaccination in the programme, simultaneously administered with DTP-IPV-Hib vaccine, had little influence on this increase. The Netherlands Vaccination Programme has a very favourable risk balance.

Key words:
Adverse Events Following Immunisation, AEFI, Vaccination Programme, Safety Surveillance, Childhood Vaccines

Acknowledgements

We are indebted to the clinic staff and other reporters of adverse events, and to all other people willing to share information, especially the parents of children with an adverse event following vaccination.

Abbreviations

AE	Adverse Event
AEFI	Adverse Event Following Immunisation
AGS	Adreno Genital Syndrome
aK	Acellular pertussis vaccine
AMK	Advice centre and social services for child abuse and neglect
AR	Adverse Reaction
BCG	Bacille Calmette Guérin vaccine
BHS	Breath Holding Spell
BMR	Measles Mumps Rubella vaccine (MMR)
CB	Child Health Clinic (consultatiebureau)
CBG	Medical Evaluation Board of the Netherlands
CBS	Statistics Netherlands
CHT	Congenital Hypothyroidism
CIb	Centre for Infectious Disease Control (of RIVM)
CIE	Centre for Infectious diseases Epidemiology (of RIVM)
DM	Diabetes Mellitus
DKTP	Diphtheria Pertussis (whole cell) Tetanus Polio vaccine (DPTP)
DTP	Diphtheria Tetanus (inactivated) Polio (vaccine)
DPTP	Diphtheria Tetanus (whole cell) Pertussis, (inactivated) Polio (vaccine)
EPI	Expanded Programme on Immunisation
EMEA	European Medicines Agency
GGD	Municipal Public Health Department
GP	General Practitioner, Family physician
GR	Health Council
HepB	Hepatitis B (vaccine)
HBIg	Hepatitis B Immunoglobulin
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HHE	Hypotonic Hyporesponsive Episode (collapse)
Hib	*Haemophilus influenzae* type b (vaccine)
IGZ	Inspectorate of Health Care
ICH	International Conference on Harmonisation
IPV	Inactivated Polio Vaccine
ITP	Idiopathic Thrombocytopenic Purpura
JGZ	Child Health Care
LAREB	Netherlands Pharmacovigilance Foundation
LWW	Netherlands Paediatric Surveillance System for SIDS
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
PEA	Provincial Immunisation Administration (registry)
PKU	Phenyl Ketonuria
PMS	Post Marketing Surveillance
PRP-T	Polyribosil Ribitol Phosphate Tetanus conjugate vaccine

RIVM	National Institute for Public Health and the Environment
RVP	Netherlands Vaccination Programme
SAE	Serious Adverse Event
TBC	Tuberculosis
WHO	World Health Organisation

Contents

Samenvatting

Vermoede bijwerkingen van vaccinaties van het Rijksvaccinatieprogramma (RVP) worden in Nederland centraal geregistreerd en beoordeeld door het RIVM sinds 1962. De bewaking van de veiligheid van het RVP gebeurde vanaf 1984 tot 2003 in nauwe samenwerking met de Gezondheidsraad (GR). Deze taak is vanaf 2004 overgenomen door een nieuw ingestelde klankbordgroep. De telefonische informatiedienst van het RIVM is een belangrijk instrument in dit passieve bewakingssysteem. In het jaarlijkse RIVM-rapport zijn alle meldingen opgenomen, die ontvangen zijn in één kalenderjaar, ongeacht het oorzakelijke verband met de vaccinatie. Dit rapport over 2006 is het dertiende jaarrapport.
Van de meldingen kwam 90% telefonisch binnen. Meldingen kwamen merendeels vanuit de Jeugdgezondheidszorg (77%). Nadere gegevens van anderen dan de melder, bijvoorbeeld van ouders, huisarts of ziekenhuis werden in 88% van de meldingen verkregen. Na aanvulling en verificatie werd een (werk)diagnose gesteld met een causaliteitbeoordeling door artsen van het RIVM. Deze beoordeling werd meestal (93%) alleen telefonisch aan de melder teruggerapporteerd. Schriftelijk verslag van geselecteerde, ernstigere of gecompliceerde ziektebeelden, werd naar alle medisch betrokkenen gestuurd.
In 2006 zijn 1159 meldingen ontvangen, over 1059 kinderen, op een totaal van meer dan 1,4 miljoen vaccinatiemomenten. Twee meldingen waren niet te beoordelen wegens ontbrekende informatie. 875 Meldingen (76%) werden als bijwerking beoordeeld met mogelijk, waarschijnlijk of zeker causaal verband met de vaccinaties. Een toevallige samenloop werd aangenomen bij 282 (24%) meldingen.
Van de 574 gemelde mildere, zogenaamde “minor” algemene ziekte-, huid- of lokale verschijnselen werd 71% (409) als mogelijke bijwerking geduid. Gemelde zogenoemde “major” postvaccinale gebeurtenissen (585) werden in 80% (466) als mogelijke bijwerking beschouwd. Deze “major” verschijnselen betreffen de rubrieken “ziek-major”, stuipen, collaps (flauwtes), verkleurde benen, persistent screaming (≥3 uur aanhoudend krijsen), encefalopathie/-itis (hersenlijden/-ontsteking) en sterfgevallen. Voorts waren er enkele major lokale verschijnselen.
Verkleurde benen (124) hadden op 5 na een mogelijke causale relatie met de vaccinaties.
Collaps, waaronder atypische en onvolledige episodes, werd 76 maal vastgesteld, in 16 gevallen zonder oorzakelijk verband. Daarnaast waren er enkele breath-holding-spells (11), 3 keer zonder oorzakelijk verband, en flauwvallen (82) in oudere kinderen.
Stuipen (63) gingen op 6 na alle gepaard met koorts. Van de convulsies werden er 45 als mogelijke bijwerking beoordeeld. Van de 19 atypische aanvallen hadden er 10 een mogelijk causaal verband. Epilepsie (3) werd in geen van de meldingen als bijwerking geduid, maar als ongerelateerd aan de vaccinatie.
Persistent screaming (61) werd in 57 gevallen als bijwerking beschouwd.
Koorts van ≥40,5°C was de werkdiagnose bij 53 kinderen uit de “ziek-major”-groep, op 9 na alle beschouwd als mogelijke bijwerking. Van de 58 andere beelden uit de “ziek major” groep was er 22 keer een mogelijk causaal verband. Dit betrof vaccinitis (12) gepaard aan

zeer hoge koorts (≥40,5°C), tekort aan bloedplaatjes (Idiopathische Trombocytopenische Purpura, n=5), artritis/osteomyelitis/JIA (3), apneu(1) en rillingen (1).
Er waren 6 abcessen, allemaal na DKTP-Hibvaccinatie. Van één abces is bekend dat er gekweekt is; deze was positief voor hemolytische streptokokken groep A. In 2006 is één kind met encefalopathie /-itis gemeld, niet causaal gerelateerd aan de prik, maar berustend op een andere oorzaak.
De zes sterfgevallen die in 2006 zijn gemeld, zijn alle na uitgebreide evaluatie als coïncidentele gebeurtenis beoordeeld. Bij vier kinderen is obductie verricht; hierdoor is bij één kind een myocarditis geconstateerd. Één kind was reeds bekend met een stofwisselingsstoornis en is mogelijk aan de gevolgen van een infectie overleden. Een ander kind had een aangeboren hartafwijking met asplenie; bij obductie werden geen aanwijzingen voor een oorzaak van het overlijden gevonden. Dit was ook het geval bij het vierde geobduceerde kind. Bij de twee andere kinderen is de diagnose klinische wiegendood en ARDS gesteld.
De meeste meldingen (736) betroffen gelijktijdige vaccinaties tegen difterie, kinkhoest, tetanus, polio (DKTP) en tegen *Haemophilus influenzae* type b infectie (Hib). Bof, mazelen, rodehond (BMR) vaccin was betrokken in 310 van de meldingen, waarvan 290 maal gecombineerd met andere vaccins. In 74% was er een mogelijke causale relatie met deze vaccinaties. Dit was 76% voor de andere vaccin(combinatie)s.
Vergeleken met 2005 was er een stijging in het aantal meldingen. Deze is waarschijnlijk toe te schrijven aan verminderde onderrapportage. Mogelijk heeft de gefaseerde overgang naar een DKTP-Hibvaccin met vijf kinkhoestcomponenten een rol gespeeld. De introductie van het Pneumokokkenvaccin, gelijktijdig gegeven met het DKTP-Hibvaccin, heeft weinig invloed gehad op deze toename.
Het totaal aantal bijwerkingen moet in relatie gezien worden met het grote aantal verrichte vaccinaties, met meer dan 1,4 miljoen prikmomenten en de bijna zeven miljoen toegediende vaccincomponenten. De grote gezondheidwinst die de vaccinaties van het RVP oplevert, weegt op tegen de mogelijke bijwerkingen.

Summary

Adverse Events Following Immunisation (AEFI) under the National Vaccination 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 24h-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 2006 is the thirteenth annual report.
The majority of reports (90%) came in by telephone. Child Health Clinic staffs are the main reporters (77%). Parents, GP's and/or hospital provided additional data on request (88%). RIVM made a (working) diagnosis and assessed causality after supplementation and verification of data. The assessment has been communicated to the reporter, usually by phone (93%). Written assessments of selected more serious or complicated events, were sent to all medical professionals involved.
In 2006, on a total of over 1.4 million vaccination dates, 1159 AEFI were submitted, concerning 1059 children. Of these only two were not classifiable because of missing information. Of the classifiable events 875 (76%) were judged to be possibly, probably or definitely causally related with the vaccination (adverse reactions) and 282 (24%) were considered coincidental events.
So-called "minor" local, skin or systemic events were assessed in 574 cases with 409 reports (71%) 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 585 cases. In 80% (466) these were considered possible adverse reactions.
Discoloured legs were reported 124 times with possible causal relation in all but five.
Collapse, including atypical and incomplete episodes, was diagnosed 76 times, in only 16 cases without causal relation. Eleven breath holding spells were reported, in eight with inferred causality and 82 times fainting in older children.
Convulsions were diagnosed in 63 cases, in all but 6 with fever. Of the convulsions 45 were considered causally related. Atypical attack (19) had possible causal relation in 10 of cases.
Epilepsy (3) was considered not causally related with the vaccinations in all instances.
Of persistent screaming 57 out of 61 reports were considered adverse reactions.
Fever of $\geq$40.5°C was the working diagnosis in 53 reports of the major-illness group, in all but 9 with inferred causality. Of the other 58 major-illness cases 22 had a possible causal relation. These events were "vaccinitis" (12) all with very high fever ($\geq$40.5^{o}C), ITP (5), arthritis/osteomyelitis (3), apnoea (1) and chills (1).
There were 6 abscesses, all occurring after DTP-IPV-Hib. One culture was positive for Haemolytic Streptococcus group A.

One case of encephalopathy /-itis was reported in 2006, not induced by the vaccination but considered coincidental.
In 2006 all six reported deaths were considered chance occurrences after thorough assessment. Four children were examined post mortem. One child had myocarditis, one child was known with a metabolic disorder and an infection may be have been fatale. One child had a congenital heart anomaly, but obduction showed no cause of death. One child is diagnosed as SIDS. Of the other two children one died of ARDS and one was diagnosed as clinical SIDS because no autopsy was performed and there was no plausible explanation for diagnosed as death.
Most frequently (736) reports involved simultaneous vaccinations against diphtheria, pertussis, tetanus, polio (DPTP) and *Haemophilus influenzae* type b infections (Hib). Measles, mumps and rubella (MMR) vaccine was involved 310 times, 290 times with simultaneous other vaccines. In 74% of these reports there was possible causal relation with the vaccination(s). For the other vaccine combinations this percentage was 76%.
In 2006 the number of reports increased compared to 2005. This was probably due to reduced underreporting. Perhaps the phased introduction of a DTP-IPV-Hib vaccine with five pertussis components was of some importance. The addition of the Pneumococcal vaccine to the programme, simultaneously administered with DTP-IPV-Hib in infants, had little influence on this rise.
The total of 1159 reports should be weighted against the large number of vaccines administered, with over 1.4 million vaccination dates and nearly seven 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. Safety surveillance is even more important in the programmatic use of preventive interventions, especially when young children are involved. In the Netherlands the National Institute for Public Health and the Environment (RIVM) has the task to monitor adverse events following immunisation (AEFI) under the National Vaccination Programme (RVP). This programme started in 1957 with adoption of a passive safety surveillance system in 1962.
Since 1994 RIVM has reported annually on adverse events. These annual reports are based on the year of notification. They include all reported events, irrespective of severity of symptoms or causal relationship with the vaccination. Reported events are ordered by nature and severity of the symptoms and by causal relation. The present report contains a description of the procedures for soliciting notifications, verification of symptoms, diagnosis according to case definitions, and causality assessment for 2006. It also includes a description of the background, organisation and procedures of the National Vaccination Programme and the embedding in the Child Health Care System (JGZ).
We will discuss the effect of the introduction of pneumococcal conjugate vaccine (PCV7), simultaneously administered with an acellular DTP-IPV-Hib vaccine for infants born from April 2006 onwards. For children offering HepB vaccination a hexavalent DTP-IPV-Hib-Hep was implemented at all time intervals to avoid giving three vaccinations at the same time. This resulted in an extra dose for HepB. Halfway 2006 an acellular DTP-IPV vaccine replaced the separate vaccinations of DT-IPV and aP at four years of age. Reports in the current year have been carefully monitored for unexpected, unknown, new severe or particular adverse events and to changes in trends and severity.
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 2006 and compare them with previous years.
This thirteenth RIVM report on adverse events is only issued in English. The summary and aggregated tables will be posted on the RVP website, www.rvp.nl.

2 The Netherlands Vaccination Programme

2.1 Vaccines and schedule

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

Box 1. Schedule of the National Vaccination Programme of the Netherlands in 2006

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

[a] = for children born from HepB carrier mothers from 1 January 2006

[b] = for children born from April first 2006

[c] = halfway 2006 DTP-IPV

In the year under report the pneumococcal conjugate vaccine was introduced. [1]
HepB vaccination is only offered to children of parents native from countries with moderate and high risk of hepatitis B carriage and to children of HBsAg positive mothers. [2] For this last group an additional neonatal HepB vaccination was introduced. To avoid three vaccinations at the same time, children offering HepB are vaccinated with DTP-IPV-Hib-HepB at 2, 3, 4 and 11 months.
BCG vaccination is not included in the RVP. Vaccination is however offered free of charge to children with higher risk of acquiring tuberculosis when travelling to or staying in countries with a high prevalence. Usually BCG vaccination takes place in the second half-year of life. [3] 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. [3] For the RVP the age limit is 13 years.
Vaccines for the RVP are supplied by NVI and are kept in depot at a regional level at the Provincial Immunisation Administration (PEA). [3,4] The PEA is responsible for further distribution to the providers. It also has the task to implement and monitor cold chain procedures at the Child Health Clinics (CB) and Municipal Health Services (GGD). The Medical Consultant of the PEA (MAE) promotes and guards programme adherence.
The databases of the PEA contain name, sex, address and birth date of all children up till 13 years of age. The databases are linked with the municipal population registers and are updated regularly or on line, for birth, death and migration. All administered vaccinations are entered in the databases of the PEA on individual level.

Summarised product characteristics of all used vaccines in 2006 are in Appendix 2 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. [5] Up till four years of age (pre school) children attend the Child Health Clinic (CB) regularly. During these visits physical check-ups are performed. These include full medical history and growth and developmental screening at appropriate ages and tests for vision and hearing. The child is seen depending on age specific problems. At school entry the Municipal Health Service (GGD) takes over. From then on the Child Health Care gets a more population-based approach, with special attention to risk groups and fewer individual check-ups.
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 shot with DT-IPV and aP 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 [6,7,8,9,10] (Accurate numbers on birth cohort 2003-2005 have not been released as yet).

2.3 Safety surveillance

The surveillance of the RVP is an acknowledged task of the National Institute for Public Health and the Environment (RIVM): both safety surveillance and surveillance of effectiveness are performed by Epidemiology and Surveillance (EPI), independently from vaccine manufacturers. [11] EPI is part of the Centre for Infectious Disease Control (CIb) of RIVM.
Requirements for Post Marketing Surveillance of adverse events have been stipulated in Dutch and European guidelines and legislation. [12,13] The World Health Organisation (WHO) advises on monitoring of adverse events following immunisations (AEFI) against the target diseases of the Expanded Programme on Immunisation (EPI) and on implementation of safety surveillance in the monitoring of immunisation programmes. [14] The WHO keeps a register of adverse reactions as part of the global drug-monitoring programme. [15] Currently

there are several international projects to achieve increased quality of safety surveillance and to establish a register specifically for vaccines and vaccination programmes. [16,17,18]
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. [19,20] Not only true side effects but also events with only temporal association with vaccination may jeopardise uptake of the vaccination programme. [21] 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 sequelae of pertussis infection. [22] Also in Eastern Europe the diphtheria epidemics are (mainly) the result of anxiety about safety of vaccination (procedures). [23] But also recently concerns about safety rather than actual causal associations caused cessation of the hepatitis B programme in France. [24,25] 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. [19,26,27,28,29,30,31,32,33,34] Subsequent (local) measles epidemics have occurred. [35,36,37,38]
In the Netherlands the basis for the safety surveillance is an enhanced passive reporting system, based on a telephone service. Professionals call for consultation and advice on vaccination matters like schedules, contra-indications, precautions and adverse events. Reporting can also be done by regular mail, fax or e-mail. The annually distributed vaccination programme (Appendix 1) encourages Health Care providers to report adverse events to RIVM, giving address, telephone number, fax number and email address. Most municipal and regional Child Health organisations, which provide the vast majority of vaccinations, have explicit guidelines for notifying AE 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.
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 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 2). Vaccine failures may result from programmatic errors and professionals are therefore invited to report these also.

Box 2. Reporting criteria for AEFI under the National Vaccination Programme

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

All notifications are accepted, registered and assessed by RIVM, irrespective of nature and severity of symptoms, diagnoses or time interval. No discrimination is made for formal reports or for consultations regarding adverse events. See for detailed description on procedures chapter 3.
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.[39,40,41,42,43,44,45,46,47,48,49,50,51] 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. [52]

3 Materials and methods

3.1 Post vaccination events

Events following immunisations do not necessarily have causal relation with vaccination. Some have temporal association only and are in fact merely coincidental. [19,20,4] 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 immunisation against one or more diseases.
- Vaccination: all activities necessary for vaccine administration.
- Post vaccination event or Adverse Events Following Immunisation (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 3). [3,39,53,54]

Box 3. 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 Notifications

All incoming information on adverse events following immunisations (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 2). 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 (see also paragraph 4.3). These reports are termed *compound*. If the notification is about different vaccination dates, the report is classified under the most appropriate vaccination date, as single if the events concerned consist of only minor local or systemic symptoms. If however there are 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 notifications on different vaccinations of the same child are time spaced, 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

3.3 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”.

3.4 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 GP or hospital is contacted to verify symptoms or in case of incomplete records or severe, complex or difficult to interpret events.

3.5 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 the ten different categories listed and clarified below (Box 5). 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: consist of inflammatory symptoms and other signs around the injection sites which are classified as minor if they are not extensive and are of limited duration. Atypical or unusual mild or moderate symptoms at the injection site are included in this category. Inflammation that is very extensive or extremely prolonged will be listed under major-local reactions, as well as abscess or erysipelas. In cases with accompanying systemic symptoms, the event is only booked in this category if local symptoms prevail or are considered major.
- General illness: includes all events that cannot be specifically categorised in the other event categories. For instance fever, respiratory or gastric-intestinal symptoms, crying, irritability, change in sleeping pattern or feeding behaviour, upper airway symptoms, rash illness, etceteras, fall under this category. Mild or moderate symptoms are listed under minor general illness, severe symptoms under major general illness. Fever of 40.5°C and over is listed, by consent, as major general illness, except if associated with febrile convulsion or as part of another specific event.
- Persistent screaming: (sudden) screaming, non-consolable and lasting for three hours or more, without one of the other specific diagnostic groups being applicable. This is considered a major event.
- General skin symptoms: skin symptoms that are not part of general (rash) illness and not considered extensions of a local reaction fall in this category. Like exanthema or other rashes as erythema, urticaria, that are not restricted to the injection site. Circumscript lesions distant from the injection site are included and the harlequin syndrome is booked

under skin symptoms as well. Some mild systemic symptoms may be present. Subdivision is made according to severity in minor and major if applicable.

- Discoloured legs: symptoms are diffuse or patchy discoloration of the leg(s) and/or leg petechiae, with or without swelling. Extensive local reactions are not included. By consent discoloured legs is a major adverse event.
- Faints: collapse reactions (HHE, hypotonic hyporesponsive episode), a sudden pallor, loss of consciousness and loss of muscle tone are included unless these symptoms are explicable as post-ictal state or part of another disease entity. If symptoms are incomplete or atypical this is added as an annotation. In collapse following fierce crying that suddenly stops with or without the clear-cut breath holding phase, specific annotation will be made too. In case of classical breath holding spell with no or very short period of pallor this event will be listed under faints as a separate group. Fainting in older children is listed as a separate group within this category also. Just pallor or apathy or prolonged sleeping or limpness only is not considered collapse reaction and are grouped under general illness.
- Fits: convulsions are all episodes with tonic and/or clonic muscle spasms and loss of consciousness. There is discrimination by body temperature in non-febrile and febrile convulsions. If fever is $\geq$38.5°C it is booked as febrile convulsion unless the convulsion is symptomatic for meningitis or for other illness. Febrile seizures of more than 15 minutes or asymmetrical or recurring within 24 hours are complex as opposed to simple (classic). Definite epileptic fits or epilepsy are included in this category also. Unspecifiable atypical attacks are a separate group under fits. These are paroxysmal occurrences without the specific criteria for collapse or convulsions or could not be diagnosed definitely as chills or myoclonics e.g. Nocturnal myoclonics are not included, neither are episodes of irritability, jitteriness or chills; these are grouped under general illness.
- Encephalitis or encephalopathy: children younger than 24 months with encephalopathy have an explicit or marked loss of consciousness for at least 24 hours which is not caused by intoxication and not explicable as post-ictal state. In children older than 24 months at least 2 of the 3 following criteria must be fulfilled:
  - change in mental status like disorientation, delirium or psychosis not caused by drugs;
  - marked decrease in consciousness not caused by seizures or medication;
  - seizures with (long lasting) loss of consciousness.

  Also signs of increased intra-cranial pressure may be present. In encephalitis, apart from the symptoms of encephalopathy there are additional signs of inflammation as fever and elevated cell counts in the cerebrospinal fluid.
- Anaphylactic shock: circulatory insufficiency with hypotension and life threatening hypoperfusion of vital organs with or without laryngeal oedema or bronchospasm. This reaction should be in close temporal relation with intake of an allergen and with type I allergic mechanism involved. Urticaria or wheezing alone is not included.
- Death: all reported children who died following immunisation are included in this category and not under one of the other listed categories.

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

3.6 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).
After establishing to what extent the vaccine or vaccination has contributed to the event, its causality will be classified under one of the five listed different categories (Box 7).
Certain (conclusive, convincing, definite), if the vaccine is proven to be the cause or if other causes are ruled out definitely; there should be a high specificity of the symptoms and a fitting interval. *Probable* causal relation, if there are no signs of other causes, there is a fitting interval and a satisfactory biologic plausibility of vaccine/vaccination as cause of the event. If, however, other possible causes exist or the time interval is only just outside the acceptable limits or symptoms are rather unspecific causal relation is classified as *possible*. If a certain, probable or possible causal relation is established, the event is classified as adverse reaction or side effect.

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 causal relation is considered (highly) *improbable* there is implausible temporal relation or established other cause of the event. The event is then considered coincidental or chance occurrence. This category includes also events without any causal relation with the vaccination. If data are insufficient for a (working) diagnosis and causality assessment, the event is listed under *unclassifiable*.
Generally it is evaluated as well, to what extend the vaccine or vaccination has contributed to the event and how. This is especially important in case faulty procedures are involved or individual risk factors exist. This may have implications for management of side effects or contraindications. See also paragraph 3.1 and Box 3.
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.

3.7 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 likelihood of a causal relation is given during the notifying telephone call or a later feedback call. 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 is done to ascertain that everyone involved gets the same information and to make the assessment (procedure) transparent. This document is filed together with the other information on the case.

3.8 Annual reports and aggregated analysis

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

3.9 Health Council and expert panel

Since 1984 the Health Council (GR) advises the Minister of Health, Welfare and Sport on the safety of the National Vaccination Programme. A permanent committee has been appointed. Up till 2003 GR has based their safety advice on the re-evaluation of the formal written assessments by RIVM, the international medical literature and the aggregated reports of all notifications assessed by RIVM. Summarised reassessments of the GR committee have been published in annual GR reports to the Minister of Health, Welfare and Sport. [55,56,57] As off 2003 an internal GR realignment of the tasks of this committee resulted in stopping the individual reassessments, so the footing of the advice on the safety of the RVP was no longer based on that aspect.
RIVM very much values a broad scientific discussion on particular reported events and therefore has set up an expert panel since 2004. Currently this group includes specialists on paediatrics, neurology, immunology, pharmacovigilance and microbiology. Written assessments are reassessed on diagnosis and causality.

3.10 Quality assurance

Assessment of adverse events is directed by standard operating procedure.
There have been internal inspections up till 2002 and the GR regular audits over the years up till 2003. This has been commented upon in the GR report over 2001-2003.
Severe, complex, controversial and otherwise interesting events are discussed regularly in clinical conferences of the physicians of RIVM.

3.11 Medical control agency and pharmacovigilance

RIVM sends expedited reports on so called serious adverse events (SAE) to the manufacturers and to Lareb, thus allowing the Dutch medical control agency (CBG) to fulfil its obligations towards WHO and EMEA. Lareb sends reports directly received from other reporters on programmatically used vaccines to RIVM.
At the same time RIVM sends line listings of all adverse events (AE) every three months to the specific vaccine manufacturers that contribute to the National Vaccination Programme.

4 Results

4.1 Number of reports

In 2006 RIVM received 1159 notifications of adverse events, involving 1059 children.
57 Notifications were multiple, resulting in 116 reports. 33 Notifications were compound.
Two notifications were compound and multiple, resulting in 10 reports. (Table 1). Multiple and compound reports are listed under the respective event categories. See paragraph 3.2 for definitions.

Table 1. Number and type of reports of notified AEFI in 2001-2006

notifications 2006	children	adverse event reports	reports 2005	2004	2003	2002	2001
single	967[a]	967	890	1756	1166	1174	1178
multiple	57[b]	116	99	280	151	111	133
compound	33[c]	66	44	80	41	34	16
compound and multiple	2	10	3	25	16	13	4
Total 2006	1059	1159	1036	2141	1374	1332	1331

[a] 27 children had also reports in previous (22) or following (5) years; these are not included
[b] two children with triple reports
[c] all children had double reports

From 1994 onwards comparisons of numbers are valid because the criteria for recording have been consistent.
For the period 1994 till 2004 there was a gradual increase in number of reported adverse events due to reduced underreporting, introduction of new vaccines and changes of the schedule. [40,41,42,43,45,46,48,49]
The increase in 2004 followed adverse publicity on the safety of the DTP-IPV-Hib vaccine starting in the first week of January 2004. [50] In March 2004 the GR advised the Minister to change to an acellular pertussis containing vaccine as soon as possible. [58] In 2005, for the first time in years, the number of reports went down, both for single events as for compound and multiple events following the introduction of DTP-IPV-Hib with three acellular pertussis components. In 2006 we gradually switched to an infant combination vaccine with five pertussis components. Also we added the seven valent pneumococcal conjugate vaccine (PCV7) to the programme for children born from April first onwards; numbers increased significantly (Table 2).

Table 2. Number of reported AEFI per year[a] (statistically significant changes in red)

year of notification	total[b]
1984	310
1985	325
1986	350
1987	325
1988	390
1989	440
1990	375
1991	340
1992	440
1993	496
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**

[a] before 1994 registration according to year of vaccination and from 1994 onwards to year of notification

[b] up till 1993 total numbers are estimates; from 1994 onwards totals are accurate counts

4.2 Reporters, source of information and feedback

Child Health Clinics accounted for 894 reports (77%). In 2001-2005 this varied between 75% and 81%. Parents of 121 children (10.4%) were the primary reporters (range 8.2%-12.6% in 2001-2005). The share of the Municipal Health Service in reporting was 6.9%. In 2001-2005 this fluctuated from 2.0% to 7.3%. The share of other report sources was more or less stable (detailed information in Figure 1 and Table 3).

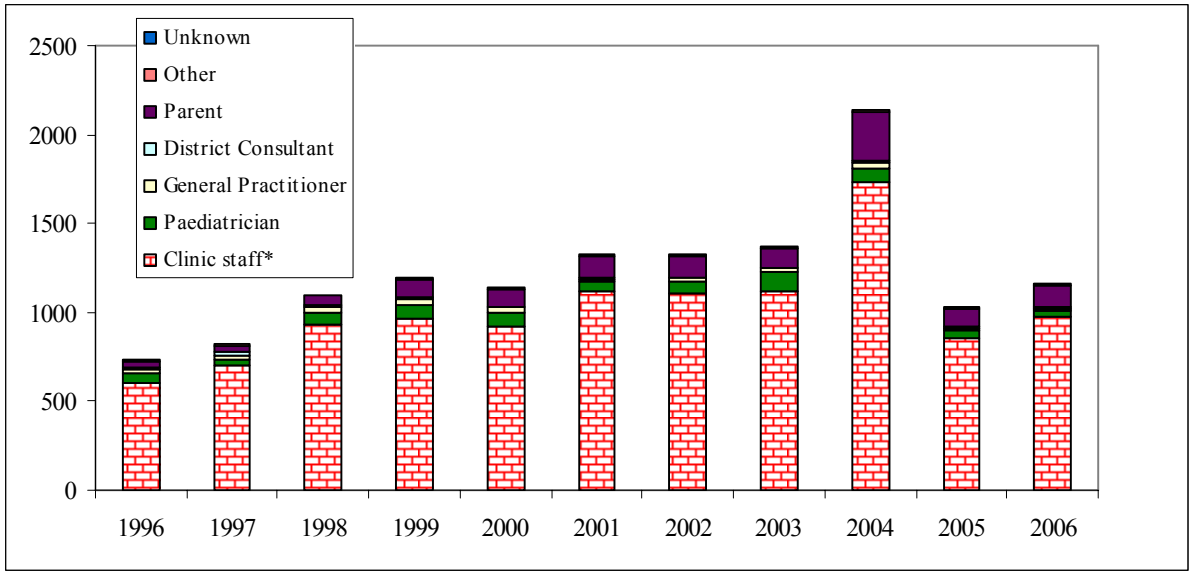

Figure 1. Reporters of adverse events following vaccinations under the RVP 1996-2006

* = Child health Care and Municipal Health Service

As in previous years the vast majority of reports reached us by telephone (Table 3). We received 111 (9.6%; range 3.8%-12.9% for 2001-2005) written reports.

Table 3. Source and reporting route of AEFI in 2001-2006

		2001	2002	2003	2004	2005	2006	*tel*	*mail*[a]
Clinic staff	Physician	794	791	741	1199	547	561	*532*	*29*
	Nurse	290	282	337	486	228	333	*319*	*14*
Paediatrician		56	61	108	84	48	35	*31*	*4*
General Practitioner		18	17	22	24	13	11	*11*	-
Municipal Health Service		31	39	39	44	76	80	*51*	*29*
District Consultant		11	8	5	21	12	8	*8*	-
Parent		115	121	113	271	102	121	*88*	*33*
Other		14	13	9	12	10	10	*8*	*2*
Unknown		2	-	-	-	-	-	-	-
total		1331	1332	1374	2141	1036	1159	*1048*	*111*
(% written)		(3.8)	(4.9)	(7.9)	(12.9)	(11.3)	(9.6)		

[a] including e-mail (34) and fax (9) reports

In 2006 the reporter was the sole informer in 12%. Additional information was received in 88%, both spontaneously and requested (range 72-87% for 2001-2005). The clinics (child health clinics, municipal health service and refugee clinics) supplied information in 91.2%, compared to 93-94.5% in the previous three years. Parents were contacted in 90.6%, (range 76%-90% for 2001-2005), including reports in which the parents were the sole informers (55). Hospital specialists supplied information in 18% of the reports (range 16%-24% for 2001-2005). See for details Table 4.

Table 4. Information sources and type of events in reported AEFI in 2006

																Total	(%)
info ⇒	clinic*	+	+	+	+	+	+	+	+	-	-	-	-	-	-	1057	(91.2)
	parent	-	+	+	+	+	-	-	-	+	+	+	-	-	-	1050	(90.6)
	gen. pract.	-	-	-	+	+	-	+	+	+	-	-	+	-	-	51	(4.4)
	hospital	-	-	+	-	+	+	-	+	-	+	-	-	+	-	208	(17.9)
event ⇓	other	-	-	-	-	-	-	-	-	-	-	-	-	-	+	35	(3.0)
local reaction		7	78	6	4	-	-	-	-	-	2	5	-	-	-		102
general illness	minor	17	297	29	11	1	2	3	1	5	10	23	2	-	3		403
	major	4	51	23	5	4	2	-	1	1	10	7	-	2	-		111
persistent screaming		2	52	5	1	-	-	-	-	-	1	-	-	-	-		61
skin symptoms		9	65	6	4	1	1	-	-	2	1	8	-	-	-		97
discoloured legs		5	96	15	-	-	-	-	-	-	1	7	-	-	-		124
faints		35	100	27	1	-	1	-	-	-	2	3	-	-	-		169
fits		-	33	38	1	1	4	1	-	-	3	2	-	2	-		85
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-	-		-
encephalopathy/-itis		-	-	1	-	-	-	-	-	-	-	-	-	-	-		1
death		1	-	1	-	-	3	-	1	-	-	-	-	-	-		6
Total 2006		80	772	151	27	7	13	4	3	8	30	55	2	4	3		1159

* child health, school health and refugee clinic

Feedback of diagnosis and causality assessment with advice on further vaccinations is a major characteristic of the surveillance system. In many reports this is (preliminarily) achieved in the notifying phone call. In most reports further verification and additional information is necessary for final assessment. Feedback, both to professionals and parents, is mostly done by telephone. A full written assessment followed 86 (7.4%) reports (range 6%-12% for 2001-2005, Table 5). These concerned the more complex events or those causing (public) anxiety or extreme uncertainty about subsequent vaccinations.

Table 5. Feedback method and events of reported AEFI in 2001-2006

		2001		2002		2003		2004		2005		2006	
event ⇓ feedback method⇒		mail	total	mail	total	mail	total	mail	total	mail	total	mail	total
local reaction		1	90	1	120	4	123	4	129	2	93	2	102
general illness	minor	21	447	12	417	16	460	16	704	13	389	14	403
	major	14	74	20	112	51	119	33	194	30	97	23	111
persistent screaming		2	49	1	46	2	55	3	133	1	58	1	61
skin symptoms		0	73	-	104	5	104	3	106	2	82	3	97
discoloured legs		14	175	4	137	9	134	15	279	2	57	5	124
faints		34	293	20	297	35	244	25	378	6	133	14	169
fits		22	121	16	91	47	132	37	211	20	118	17	85
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		2	2	-	-	-	-	3	3	-	1	1	1
death		7	7	8	8	3	3	4	4	8	8	6	6
total 2006		117	1331	82	1332	172	1374	143	2141	84	1036	86	1159

4.3 Sex distribution

In the current year 51% of the reported cases were male, in line with the national distribution. For the years 2001-2005 this ranged between 51-54% (Table 6). Of six children the sex is not known.

Table 6. Events and sex of reported AEFI in 2001-2006 (totals and percentage males)

event ⇓	sex⇒	m%	2001 total	m%	2002 total	m%	2003 total	m%	2004 total	m%	2005 total	m%	2006 total
local reaction		47	90	43	120	49	123	48	129	46	93	51	102
general illness	minor	55	447	53	417	57	460	56	704	55	389		403
	major	59	74	52	112	57	119	53	194	52	97		111
persistent screaming		57	49	61	46	56	55	50	133	47	58	54	61
skin symptoms		53	73	51	104	51	104	53	106	49	82	54	97
discoloured legs		42	175	51	137	42	134	53	279	51	57	50	124
faints		47	268	52	270	49	210	54	318	51	75	50	169
fits		53	56	58	45	53	70	56	98	53	71	47	85
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		50	2	-	-	-	-	0	3	100	1	100	1
death		43	7	75	8	100	3	25	4	38	8	83	6
Total		51	1331	52	1332	52	1374	54	2141	52	1036	51	1159

4.4 Regional distribution

Reports reached us from all over the country but were not evenly spread. Standardisation of the rate per 1000 vaccinated infants is done according to coverage data from the PEA. In Table 7 the 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 inevitably remain 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 185,057 in 2006. [59] The reporting rate was 6.2 per 1000 vaccinated infants (DTP-IPV-Hib3) in 2006. Range for 2001-2005 is 5.5-11.4 (DTP-IPV-Hib3). There was less dispersion of the reporting rates over the different regions, compared to 2005.

Table 7. Regional distribution of reported AEFI in 2001-2006, per 1000 vaccinated infants[a] with proportionate confidence interval for 2006 (major adverse events)

	2001 (major)	2002 (major)	2003 (major)	2004 (major)	2005 (major)	2006 (major)	95% c.i. 2006 (major)
Groningen	4.5 (3.4)	4.1 (2.5)	5,4 (2.8)	16.4 (9.6)	6.4 (2.4)	7.1 (3.5)	4.96-9.23 (2.03-5.06)
Friesland	6.4 (3.2)	7.6 (4.8)	7,5 (4.4)	13.1 (7.8)	5.0 (2.9)	5.6 (2.9)	3.93-7.33 (1.72-4.18)
Drenthe	3.7 (2.0)	3.1 (2.2)	6,4 (3.7)	12.9 (10.3)	5.2 (2.6)	5.2 (2.6)	3.26-7.08 (1.23-3.94)
Overijssel	6.0 (3.3)	6.4 (3.7)	7,4 (3.3)	11.2 (5.8)	4.2 (1.6)	6.8 (3.4)	5.41-8.15 (2.45-4.40)
Flevoland	6.9 (4.1)	6.8 (3.4)	7,4 (4.2)	16.2 (9.0)	8.5 (3.6)	5.8 (2.4)	3.78-7.88 (1.12-3.77)
Gelderland	5.0 (2.9)	5.9 (3.2)	6.3 (3.0)	10.8 (5.8)	5.5 (2.3)	5.8 (2.8)	4.78-6.77 (2.08-3.46)
Utrecht	6.7 (3.4)	6.7 (3.1)	6,9 (3.2)	8.1 (4.8)	7.9 (4.5)	8.4 (5.4)	6.97-9.89 (4.27-6.61)
Noord-Holland[b]	5.0 (2.7)	4.2 (2.3)	4.6 (2.3)	9.0 (5.0)	4.7 (2.4)	5.3 (2.9)	4.33-6.20 (2.16-3.54)
Amsterdam	7.8 (3.5)	6.0 (2.6)	7.3 (4.0)	9.9 (4.2)	5.8 (2.3)	7.2 (3.8)	5.37-9.11 (2.45-5.17)
Zuid-Holland[b]	7.5 (4.0)	7.6 (3.8)	8.4 (4.5)	11.6 (6.2)	4.9 (2.4)	6.2 (2.7)	5.25-7.09 (2.12-3.34)
Rotterdam	5.4 (3.8)	5.6 (2.4)	4,7 (1.7)	6.6 (4.7)	3.7 (1.9)	4.7 (2.1)	2.99-6.39 (0.96-3.24)
Den Haag	8.9 (4.9)	6.1 (2.5)	9,7 (5.5)	9.0 (5.5)	5.5 (1.8)	4.0 (1.5)	2.42-5.63 (0.52-2.49)
Zeeland	7.7 (5.8)	7.1 (5.6)	8.5 (4.0)	14.1 (10.7)	3.9 (1.6)	5.0 (2.6)	2.75-7.21 (1.00-4.24)
Noord-Brabant	7.7 (4.3)	8.5 (4.8)	7,8 (4.2)	14.6 (8.5)	6.6 (3.2)	6.8 (3.5)	5.81-7.77 (2.77-4.17)
Limburg	8.5 (5.4)	10.3 (5.3)	8.5 (4.6)	12.0 (6.8)	4.8 (2.7)	5.7 (2.5)	4.30-7.20 (1.54-3.45)
Netherlands	6.6 (3.7)	6.7 (3.6)	7.1 (3.7)	11.4 (6.6)	5.5 (2.6)	6.2 (3.1)	5.84-6.55 (2.87-3.38)

[a] For 2003 and 2004 coverage data of the corresponding year out of Praeventis have been used; the data of 2004 are applied to 2005 and 2006 as well, because definite numbers were not available

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

The 95% confidence intervals of only two regions did not include the country's overall reporting rate. The country's average reporting rate for major events is 3.1/1000. Range for 2001-2005 is 2.6-6.6. One region had a higher reporting rate for major events only and one region a lower. We will present and compare differences in numbers of specific events in the respective paragraphs under 4.9. For more information see Table 7.

4.5 Vaccines

In the current year 95% of the notifications were about recent vaccinations. Some of the 53 late reports arose from concerns about planned booster vaccination or vaccination of younger siblings. In 11% of these cases the parents reported. The vaccine involved in these late reports was most often DTP-IPV-Hib (32) and MMR (11, of which 6 simultaneously with MenC). All reports are included in the tables.
In Table 8 scheduled and actually administered vaccines are listed. According to previous years (except 2005) reports on the first DTP-IPV-Hib dose were the most prevalent. The relative frequencies of involved vaccinations changed a little compared to previous years (Figure 3).

Table 8. Schedule and vaccines of reported AEFI in 2006

vaccine given⇒ scheduled ⇓	dtp-ipv	dtp-ipv-hib	dtp-ipv-hib+hepb	hib	pneu	mmr	mmr menc	dt-ipv	aP	dt-ipv aP	dt-ipv mmr	menc	bcg	other	total 2006	2005	2004	2003	2002	2001
at birth	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-
dose 1[a,b]	1[d]	247[e]	36[f]	-	1	-	-	-	-	-	-	-	-	-	285	205	725	462	503	515
dose 2[a,b]	-	177[h]	17[i]	-	1	-	-	-	-	-	-	-	-	-	195	153	379	229	212	229
dose 3[a,b]	-	85[j]	7	1[k]	4	-	-	-	-	-	-	-	1	1[g]	99	111	289	147	150	163
dose 4[a,b]	2[l]	120[m]	26	2[n]	2	-	-	-	-	-	-	-	1	1[g]	154	119	340	193	161	172
dose?	-	1	-	-	-	-	-	-	-	-	-	-	-	-	1	3	3	3	5	3
mmr0	-	-	-	-	-	7	-	-	-	-	-	-	-	-	7	10	1	8	-	4
mmr1+menC	-	-	-	1	3	16[o]	201[p]	-	-	-	-	4	1	-	226	246	225	173	150	139
dt-ipv5+aP[c]	-	-	-	-	-	-	-	3	-	92	-	-	-	3[q]	98	114	90	78	67	41
dtp6+mmr2	1	-	-	1	-	-	-	-	-	-	83	-	-	3[r]	88	62	62	37	35	47
menc	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	19	34	38	-
other	-	-	-	-	-	-	-	1[s]	-	-	1[t]	-	-	4[r]	6	8	6	10	11	18
total 2006	4	630	86	5	11	23	201	4	-	92	84	4	3	12	1159	1036	2141	1374	1332	1331

[a] usually DTP-IPV-Hib is administered. 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
[b] simultaneously with DTP-IPV-Hib(-HepB) PCV7 is added for children born from 1 April 2006 onwards
[c] from medio 2006 combined DTP-IPV
[d] with pneu
[e] 104 times with PCV7
[f] 18 times with PCV7
[g] HepB
[h] 63 times with PCV7
[i] all with PCV7
[j] 10 times with PCV7
[k] with MenC
[l] with HepB
[m] once with MenC, three times with MMR0
[n] once with DT-IPV
[o] once with aP, once with Yellow fever and HepA
[p] three times with DTP-IPV-Hib
[q] twice influenza, once HepA+Yellow Fever
[r] three times HepB, once HepA
[s] with HepB
[t] with MenC and HepB

The total number of reported adverse events after DTP-IPV-Hib doses was 736. In 2004 we received 1730 reports after DTP-IPV-Hib, while in 2005 this number was 593. The number of reports concerning DTP-IPV-Hib varied during the year, similar to previous years. There is no trend in increasing numbers, despite the changes in the vaccination programme. See Figure 2.

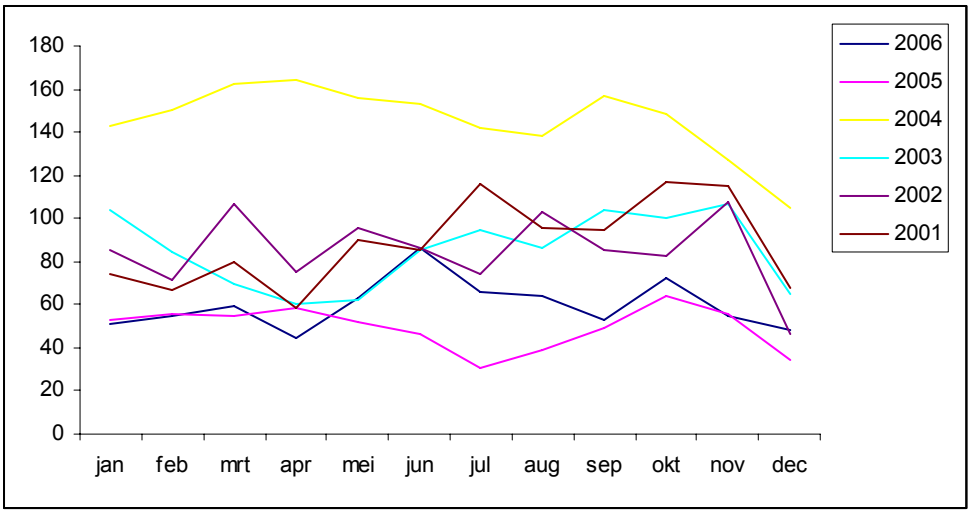

Figure 2: Absolute numbers of DTP-IPV-Hib reports per month in 2001-2006

85 Children received HepB vaccine simultaneously with DTP-IPV-Hib.
From the addition of MenC to the programme in 2002 onwards the number of AEFI following MMR1 and MenC at fourteen months increased yearly. In the current year numbers decreased. The same applies for reports after DT-IPV5 at the age of four years from the introduction of simultaneous aP in 2002 for cohort 1998 onwards.
The number of AEFI (88) following DT-IPV6/MMR2 has increased compared to 2005.
Three children were reported with events following BCG and four with non-RVP vaccines only. Further details in Table 8 and Figure 3.

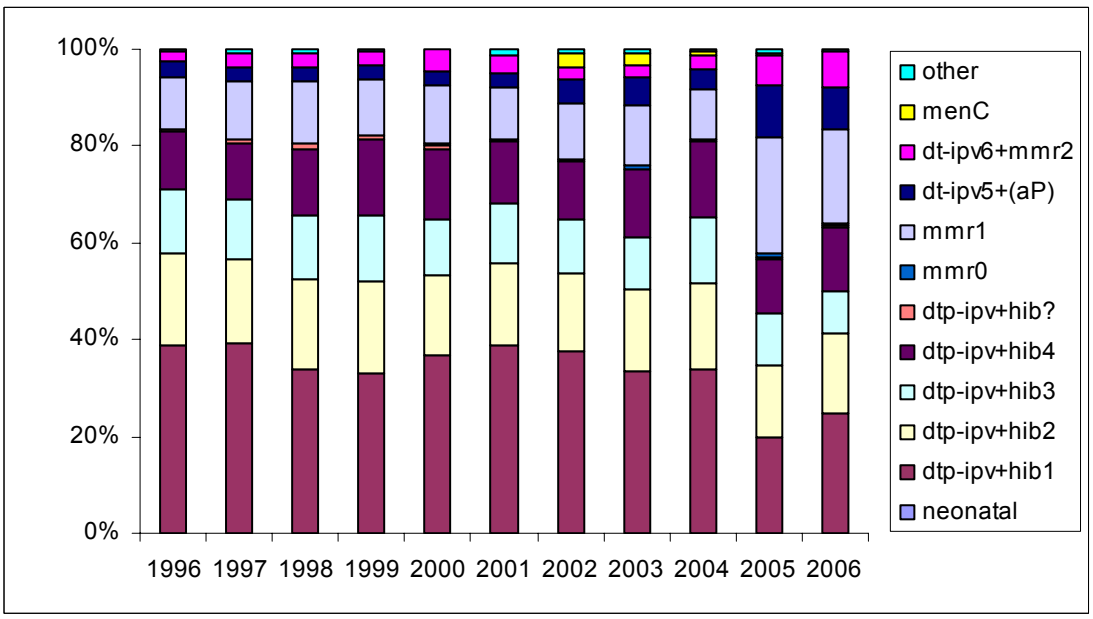

Figure 3. Relative frequencies of vaccine doses in reported AEFI in 1996-2006

Event categories are not equally distributed over the (scheduled) vaccinations (Table 9). No children with anaphylactic shock were reported. One child with encephalopathy was reported and six children who died. All events are listed here, irrespective of assumed causal relation.

Table 9. Event category and (scheduled) vaccine dose of reported AEFI in 2006 (irrespective of causality)

event ⇓ vaccine⇒[a]	at birth	dtp-ipv-hib1[b]	dtp-ipv-hib2[b]	dtp-ipv-hib3[b]	dtp-ipv-hib4[b]	dtp-ipv-hib?[b]	mmr0	mmr1 menc	dt-ipv5 aP	dt-ipv6 mmr2	other	Total 2006	2005	2004	2003	2002	2001
local reaction	-	15	7	6	27	1		7	31	6	2	102	93	129	123	120	90
general illness minor	-	102	67	45	58		5	90	16	18	2	403	389	704	460	417	447
major	-	21	9	8	19			47	2	4	1	111	97	194	119	112	74
persistent screaming	-	30	17	8	6	-	-	-	-	-	-	61	58	133	55	46	49
skin symptoms	-	13	13	8	19		2	22	10	9	1	97	82	106	104	104	73
discoloured legs	-	44	51	14	8	-	-	-	7	-	-	124	57	279	134	137	175
faints	-	52	24	5	3			3	31	51	-	169	133	378	244	297	293
fits	-	4	6	5	14			55	1		-	85	118	211	132	91	121
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	1	-	-	-	-	-	-	-	-	-	1	1	3	-	-	2
death	-	3	1	-	-	-	-	2	-	-	-	6	8	4	3	8	7
total	0	285	195	99	154	1	7	226	98	88	6	1159	1036	2141	1374	1332	1331

[a] scheduled vaccines are listed. See for more precise description Table 7 and the respective event categories

[b] pneumococcal vaccine (PCV7) was added for children born from April first onwards.

Compared to 2005, a statistically significant rise in reported adverse events is seen. However, the total is still lower than numbers for the period 2001-2004. Within and between the different event categories there are some changes. These will be commented upon in the specific event paragraphs. Absolute numbers may be deceptive as the rate depends on actual number of vaccinations and only preliminary vaccine coverage data are available for this reporting period, with no information on the timing.
The relative frequency of the different event categories has changed a little since the introduction of acellular DTP-IPV-Hib vaccine (Figure 4). General illness (minor and major) is still the largest category, with a relative frequency of around 40%. The share of faints and discoloured legs increased compared to 2005, being the first year we used an acellular DTP-IPV-Hib vaccine.

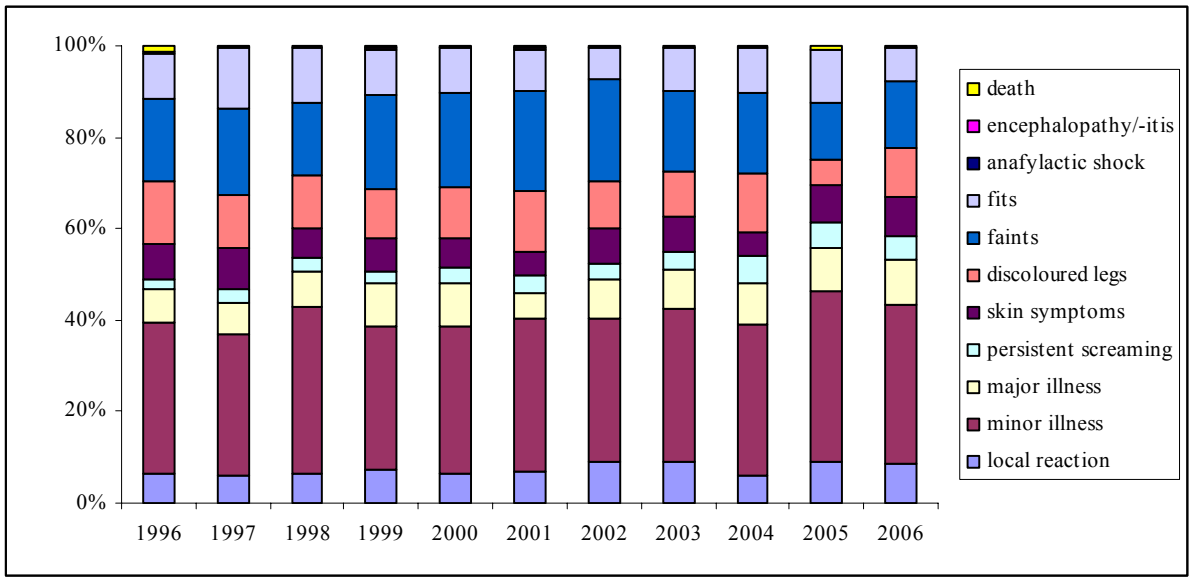

Figure 4. Relative frequencies of events in reported AEFI 1996-2006

4.6 Severity of reported events and medical intervention

The severity of reported adverse events is historically categorised in minor and major events. The number of the so-called major events was 585 of 1159 (50.5%), with positive causality in 466 (40.2%) reports. In 2001-2005 the share of major events ranged from 47.5%-57.5% with positive causality in 36.4%-49.4% (Figure 5). See also for causality paragraph 4.7.

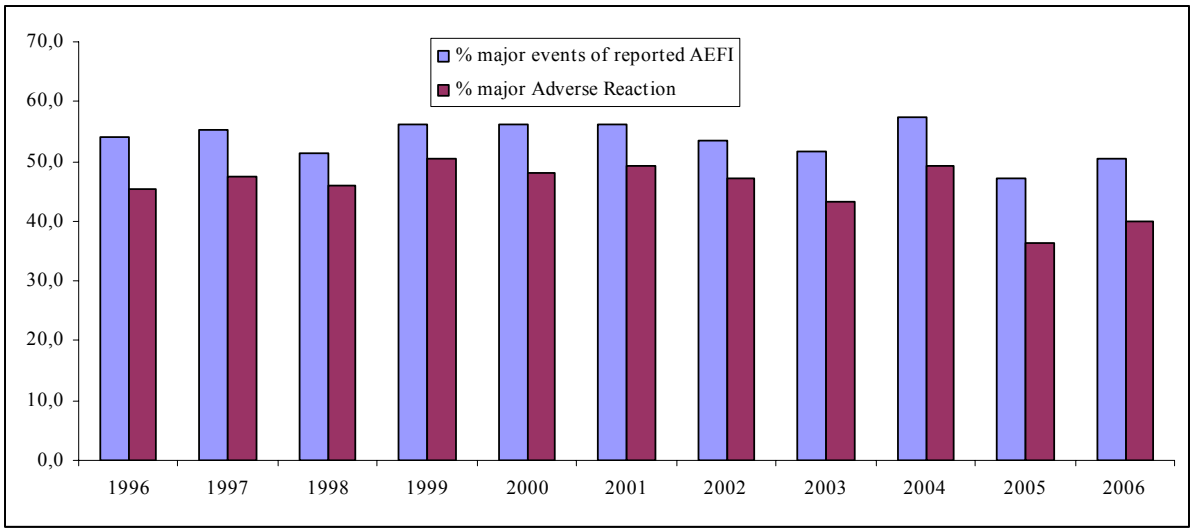

Figure 5. Proportion of reported major AEFI and major Adverse Reactions in 1996-2006

The level of medical intervention may also illustrate the impact of adverse events. In 18.3% (212) of reports either no medical help was sought or was not reported to or recorded by us (range 16-21% for 2001-2005). Parents administered paracetamol suppositories, diazepam by

rectiole or other home medication 159 times (14%; range 13-27% for 2001-2005). In Table 10 and Figure 6 intervention is shown according to highest level. In 67% parents contacted the clinic or GP, called the ambulance or went to hospital, with 9% admittance. For the five previous years these percentages varied from 57-69% and from 8-13% for hospital admittance.

Table 10. Intervention and events of reported AEFI in 2006 (irrespective of causality)

event⇓ intervention⇒		?	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		6	18	8	26	6	30	-	2	4	2	-	-	102
general illness	minor	24	60	68	45	31	122	1	21	7	17	7	-	403
	major	6	2	18	-	9	33	1	13	1	28	-	-	111
persistent screaming		5	14	22	3	5	9	-	-	1	2	-	-	61
skin symptoms		4	10	6	15	5	43	-	7	2	1	4	-	97
discoloured legs		6	25	24	17	5	31	1	4	9	2	-	-	124
faints		1	24	10	75	8	20	3	6	7	15	-	-	169
fits		1	6	3	-	1	17	9	5	11	32	-	-	85
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		-	-	-	-	-	-	-	-	-	1	-	-	1
death		-	-	-	-	-	-	-	-	-	2	-	4	6
total 2006		53	159	159	181	70	305	15	58	42	102	11	4	1159

[a] homeopathic or herb remedies, baby massage or lemon socks are included in this group, as are 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

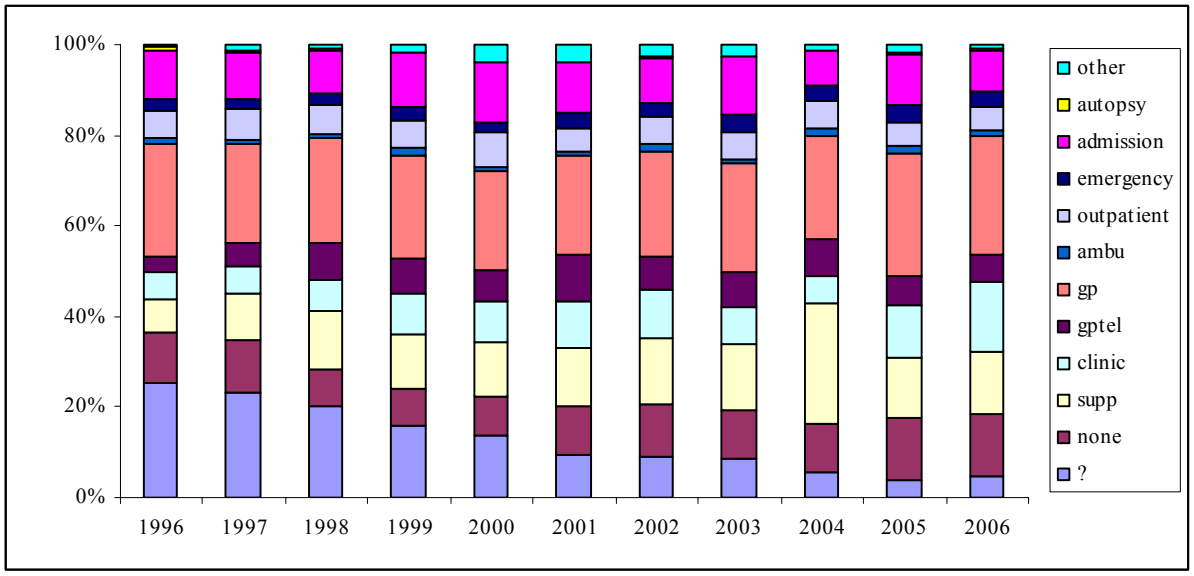

Figure 6. Highest utilized level of medical intervention for AEFI 1996-2006

4.7 Causal relation

Events with (likelihood of) causality assessed as certain, probable or possible are considered adverse reactions (AR). In 2006, 76% of reports were adverse reactions, with exclusion of two non-classifiable events. Range for 2001-2005 is 73%-83%. The other events (282) were considered coincidental with improbable or absent causal relation with the vaccinations. There are great differences in causality between the different event categories (Table 11), but over the years very consistent. See for description and more detail the specific paragraphs under 4.9 and discussion in chapter 5.

Table 11. Causality and events of reported AEFI in 2006 (% adverse reaction)

event ⇓ causality⇒	certain	probable	possible	improbable	non classifiable	total	(% AR*)
local reaction	82	13	7	-	-	102	(100)
general illness minor	-	122	153	127	1	403	(68)
major	-	11	47	53	-	111	(52)
persistent screaming	-	46	11	4	-	61	(93)
skin symptoms	-	-	60	37	-	97	(62)
discoloured legs	-	101	18	4	1	124	(97)
faints	-	138	11	20	-	169	(88)
fits	-	14	41	30	-	85	(65)
anaphylactic shock	-	-	-	-	-	-	
encephalopathy/-itis	-	-	-	1	-	1	(0)
death	-	-	-	6	-	6	(0)
total 2006	82	445	348	282	2	1159	(76)

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

Positive causality for combinations with at least one live attenuated vaccine, mainly MMR, was assessed in 74%. For vaccinations with only inactivated vaccines (DT-IPV, DTP-IPV-Hib, Hib, aP, MenC, HepB, HepA and Influenza) possible causal relation was assessed in 76% of the reports.

4.8 Expert panel

RIVM very much values a broad scientific discussion on particular reported events. Until 2004 the 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 and microbiology. Written assessments are reassessed on diagnosis and causality.
In 2006 the expert panel has focussed on 59 cases.

Table 12: Numbers of reports reassessed by the expert panel

event ⇓		Expert panel	total	(% *)
local reaction		-	102	(0)
general illness	minor	8	403	(2)
	major	23	111	(21)
persistent screaming		-	61	(0)
skin symptoms		-	97	(0)
discoloured legs		1	124	(<1)
faints		1	169	(<1)
fits		19	85	(22)
anaphylactic shock		-	-	
encephalopathy/-itis		1	1	(100)
death		6	6	(100)
total 2006		59	1159	(5)

* = % reassessments

All members of the expert panel agreed with the causality assessment of the reports, determined by the RIVM.

4.9 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 2006.

4.9.1 Local reactions

In 2006, 102 predominantly local reactions were reported, more frequently after DTP-IPV-Hib (55%) than DT-IPV and aP (36%) vaccinations (Table 13). Focussing on major reactions only, there is more emphasis on DT-IPV and aP vaccinations at four years of age. As can be expected, all reported local events were assessed causally related with the vaccination.
The majority of the reported local reactions (74) were classified as minor reactions.
28 Reports were considered major local reactions because of size, severity, intensity or duration. Common inflammation was the most prevalent aspect in 77 reports (20 considered major). 14 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 13. Local reactions and scheduled vaccines of reported AEFI in 2006 (major events)

vaccine⇒ / event⇓	dtp-ipv-hib1[a] (major)	dtp-ipv-hib2[a] (major)	dtp-ipv-hib3[a] (major)	dtp-ipv-hib4[a] (major)	dtp-ipv-Habr[a] (major)	mmr1 menc (major)	dt-ipv5 aP (major)	dt-ipv6 mmr2 (major)	Other (major)	2006 (major)	2005 (major)	2004 (major)	2003 (major)	2002 (major)	2001 (major)
moderate/ pronounced	12 (2)	3 (0)	2 (0)	22 (6)	1 (0)	5 (0)	26 (11)	5 (1)	2 (0)	78 (20)	55 (7)	60 (10)	75 (13)	54 (8)	34 (5)
abscess	1 (1)	1 (1)	3 (3)	1 (1)	-	-	-	-	-	6 (6)	13 (13)	14 (14)	6 (6)	8 (8)	13 (13)
pustule	-	-	-	-	-	-	-	-	-	-	1 (0)	1 (0)	0	1 (1)	3 (3)
atypical reaction	2 (0)	2 (0)	1 (0)	3 (1)	-	1 (0)	4 (1)	1 (0)	-	14 (2)	18 (0)	29 (0)	24 (2)	31 (3)	22 (1)
haematoma	-	-	-	-	-	-	-	-	-	-	-	2 (0)	2 (0)	2 (1)	6 (1)
nodule	-	1 (0)	-	-	-	-	-	-	-	1 (0)	4 (0)	6 (0)	4 (0)	17 (1)	6 (2)
avoidance	-	-	-	1 (0)	-	1 (0)	1 (0)	-	-	3 (0)	2 (0)	17 (1)	12 (2)	7 (0)	6 (0)
total 2006 (major event)	15 (3)	7 (1)	6 (3)	27 (8)	1 (0)	7 (0)	31 (12)	6 (1)	2 (0)	102 (28)	93 (20)	129 (25)	123 (23)	120 (22)	90 (25)

[a] pneumococcal vaccine (PCV7) was added for children born from April first onwards.

Three of the 6 abscesses were drained surgically; others drained spontaneously. Once the culture was positive for haemolytic Streptococcus Group A. Twice no culture was taken, for three abscesses this information is lacking. No faulty vaccination procedures were detected.

4.9.2 Systemic symptoms

Events that are not classifiable in one of the other specific categories are listed under general illness, depending on severity subdivided in minor or major (see paragraph 3.5).

Minor general illness

In 403 children the event was considered to be minor illness. Of these reports 31% were considered to have improbable causal relation with the vaccination. For 2001-2005 this range was 27-34% (Table 14).

67% of reported events concerned the scheduled DTP-IPV-Hib vaccinations. In 2005 this was 60%. Although rising again, it remains lower than in 2001-2004 (75-81%).

Table 14. Minor illness and scheduled vaccines of reported AEFI in 2001-2006

scheduled vaccine⇓	2001	2002	2003	2004	2005	2006	(%AR[b])
dtp-ipv-hib1[a]	158	141	152	244	88	102	(84)
dtp-ipv-hib2[a]	65	72	73	111	52	67	(70)
dtp-ipv-hib3[a]	56	41	52	104	42	45	(64)
dtp-ipv-hib4[a]	63	58	65	109	49	58	(57)
dtp-ipv-hib?[a]	1	3	2	1	2	-	-
dtp-ipv-hib4+mmr1	3	3	1	1	-	-	-
mmr0	-	-	-	-	-	5	(60)
mmr1+menC	63	51	78	90	104	90	(64)
dt-ipv5+aP	16	20	11	26	28	16	(50)
dt-ipv6+mmr2	15	8	8	14	22	18	(78)
menC	-	17	14	4	1	-	
other	7	3	4	0	1	2	(0)
total	447	417	460	704	389	403	(69)

[a] pneumococcal vaccine (PCV7) was added for children born from April first onwards.

[b] percentage AEFI considered adverse reactions

Only very few times a definite diagnosis was possible; mostly working diagnoses were used. Fever is the most prominent symptom in 135 reports, 123 times considered possibly causally related. Of the other (working) diagnoses, in 177 reports fever was an accompanying symptom. Crying was the main feature in 61 reports, predominantly following the first two vaccinations. These numbers are in line with 2001-2003 and 2005, but much lower than in 2004. Since the introduction of acellular pertussis vaccine for infants, pallor and/or cyanosis (16) and myoclonics (8) are less frequently reported. The number of rash illness is higher than before. Children with rash and fever, related to MMR (vaccinitis) are reported less frequently.
For the other working diagnoses numbers remained more or less the same over the last years (Table 15).

Table 15. Main (working) diagnosis or symptom in category of minor illness of reported AEFI in 2001-2006 (with number of adverse reactions)

symptom or diagnosis	2001	2002	2003	2004	2005	2006	AR*	symptom or diagnosis	2001	2002	2003	2004	2005	2006	AR*
fever	87	70	100	212	120	135	123	pallor and/or cyanosis	77	79	89	83	20	16	16
low temperature	5	2	2	2	6	-	-	abnormal liver enzymes	1	1	1	1	-	-	-
crying	51	51	59	157	57	61	51	rash (illness)/petechien	25	21	37	34	38	52	18
groaning	1	1	-	2	-	-	-	vaccinitis	21	20	31	31	39	24	24
irritability	5	4	-	6	7	-	-	parotitis	2	3	-	2	2	3	2
meningismus	3	1	-	-	-	-	-	infectious disease	2	1	2	2	4	2	0
hypertonia	1	1	2	3	-	-	-	swelling face/hands/feet/?	6	4	3	8	3	2	1
myoclonics	20	16	21	26	5	8	5	lymphadenopathy	3	2	1	-	3	3	2
chills	14	12	18	20	2	1	0	arthralgia/arthritis/coxitis/ limping/falling/misbalance/ pain in limbs	6	6	8	6	18	5	3
bulging fontanel	1	-	2	1	1	-	-	allergy/atopy	1	2	1	-	-	1	0
head circumference ⇑ ⇑	-	1	-	1	-	-	-	feeding problems	8	4	1	2	2	1	0
listlessness/fatigue	3	4	7	-	-	-	-	anaemia	-	1	-	1	-	-	-
drowsiness	4	2	5	4	4	5	3	vomiting/nausea	6	4	4	1	-	13	6
prolonged/deep sleep	9	7	8	6	7	14	13	stomatitis/abscess	1	3	1	-	1	3	0
behavioural problem/-illness	13	19	6	12	1	5	1	constipation/stomach-ache	-	2	1	-	2	6	0
sleeping problems	2	2	2	4	-	-	-	gastro-enteritis/diarrhoea	13	20	14	24	12	16	3
apnoea/low saturation	-	2	2	3	1	4	2	myoglobinuria?	2	7	-	4	-	-	-
asthma (attack)/cara	7	1	2	-	-	-	-	epidiydimitis/urinary tract infection/haematuria	1	1	-	1	1	1	0
airway infection	9	12	8	13	13	11	0	epistaxis	1	-	-	-	-	1	0
cough	4	6	4	4	1	-	-	headache/migraine/ dizziness	2	4	4	3	3	-	-
dyspnoea/wheezing /hyperventilation	4	2	3	6	3	3	1	eye turn/nystagmus/ squint/ anisocoria/abducensparesis /conjunctivitis/photophobia	3	4	1	2	3	4	1
pseudo croup	2	1	-	-	1	1	0	heart murmur/arrhythmia	-	-	1	1	1	-	-
tonsillitis/cold	3	-	-	2	-	-	-	lying still/frozen	9	6	4	10	-	-	-
otitis	2	1	3	-	3	2	0	sundries	7	4	2	4	3	1	0
growth disturbance	-	-	-	-	2	-	-								
								total minor events	447	417	460	704	389	403	275

* number of adverse reaction

Major general illness

Major general illness was recorded 111 times (range 2001-2005 74-194), of which 58 events were considered adverse reactions (52%). In 2001-2005 this percentage ranged between 52-65%. Of the events 46% was reported after DTP-IPV-Hib, a decrease compared to previous years. See also Table 16

Table 16. Major illness and scheduled vaccines of reported AEFI in 2001-2006

scheduled vaccine⇓	2001	2002	2003	2004	2005	2006	(%AR[b])
dtp-ipv-hib1[a]	11	14	16	26	8	21	(57)
dtp-ipv-hib2[a]	6	12	16	21	14	9	(56)
dtp-ipv-hib3[a]	13	17	8	23	13	8	(38)
dtp-ipv-hib4[a]	19	26	28	67	10	19	(47)
dtp-ipv-hib?[a]	0	0	0	1	0	-	-
mmr1+menC	20	30	28	37	45	47	(64)
dt-ipv5+aP	0	6	8	4	1	2	(0)
dt-ipv6+mmr2	1	3	3	5	4	4	(0)
menC	0	3	10	10	2	-	-
other	2	1	2	0	0	1	(0)
total	72	112	119	194	97	111	(52)

[a] pneumococcal vaccine (PCV7) was added for children born from April first onwards.

* percentage AEFI considered adverse reactions

48 Reports followed MMR, with in 29 cases assessed causality (60%, range for 2001-2005 was 29-66%). For other vaccines or combinations 45% (29) of reported events were considered to be possible adverse reactions. The range for 2001-2005 was 38%-68%.

*Table 17. Major illness and vaccines of reported AEFI in 2006(*adverse reactions)*

diagnosis⇓ vaccine⇒	dtp-ipv-hib1	dtp-ipv-hib2	dtp-ipv-hib3	dtp-ipv-hib4	mmr1 menC	dt-ipv5 aP	dt-ipv6 mmr2	other	total (AR*)
very high fever (≥ 40.5°C)	10[a]	5[b]	5[c]	13	19[d]	1	-	-	53 (42)
chills/myoclonics	-	-	-	1	1	-	-	-	2 (1)
dehydration /gastro-enteritis	1	-	-	-	3[e]	-	-	-	4 (1)
pneumonia/bronchiolitis/respiratory infection	2	-	1	2[f]	3	-	-	-	8 (0)
apneu	3[g]	-	-	-	-	-	-	-	3 (2)
meningitis	-	2[h]	1	1	-	-	-	-	4 (0)
vaccinitis/rash illness	1[h]	-	-	1	15[i]	-	-	-	17 (10)
cardiomyopathy/myocarditis/arrhythmia	-	1	-	-	1	-	-	-	2 (0)
arthritis/osteomyelitis//JIA	-	-	-	-	-	-	1	-	1 (0)
infection	1[g]	-	-	-	-	-	-	-	1 (0)
lymphadenitis colli/abcess	1	-	-	-	2	-	-	-	3 (0)
ITP	-	-	-	-	1	-	-	-	1 (1)
botulism	-	1	-	-	-	-	-	-	1 (0)
immunity disorder	-	-	1[j]	-	-	-	-	-	1 (0)
diabetes mellitus	-	-	-	-	-	-	1[k]	-	1 (0)
retardation/autism	1	-	-	1	-	-	-	-	2 (0)
anaemia/leukaemia/pancytopenia	1	-	-	-	1	1	1	-	4 (0)
visual disorder	-	-	-	-	-	-	1	-	1 (0)
cerebellar ataxia	-	-	-	-	1	-	-	-	1 (1)
vasculitis	-	-	-	-	-	-	-	1[j]	1 (0)
total 2006 (adverse reactions)	21	9	8	19	47	2	4	1	111(58)

[a] = once with HepB, once with HepB and PCV7, once with PCV7
[b] = once with HepB and PCV7, once with PCV7
[c] = once with HepB
[d] = once with DTP-IPV-Hib, once MMR only
[e] = once MenC only
[f] = once with MenC
[g] = once with HepB and PCV7
[h] = once with PCV7
[i] = once MMR only
[j] = HepB
[k] = HepA and HepB

Very high fever (≥40.5°C) was the working diagnosis in 53 cases, compared to 37-123 in 2001-2005. In 79% of these cases the fever was considered causally related to the vaccination. In the other events of major illness very high fever was an accompanying factor in 24 cases (Table 17 and 18).

Table 18. Major illness and causal relation of reported AEFI in 2006

diagnosis⇓ causality⇒	certain	probable	possible	improbable	unclassifiable	total (%AR)
very high fever (≥ 40.5°C)	-	9	33	11	-	53 (79)
chills/myoclonics	-	-	1	1	-	2 (50)
dehydration /gastro-enteritis	-	-	1	3	-	4 (25)
pneumonia/bronchiolitis/respiratory infection	-	-	-	8	-	8 (0)
apneu	-	2	-	1	-	3 (67)
meningitis	-	-	-	4	-	4 (0)
vaccinitis/rash illness	-	-	10	7	-	17 (59)
cardiomyopathy/myocarditis/arrhythmia	-	-	-	2	-	2 (0)
arthritis/osteomyelitis/JIA	-	-	-	1	-	1 (0)
infection	-	-	-	1	-	1 (0)
lymphadenitis colli/abcess	-	-	-	3	-	3 (0)
ITP	-	-	1	-	-	1 (100)
botulism	-	-	-	1	-	1 (0)
Immunity disorder	-	-	-	1	-	1 (0)
diabetes mellitus	-	-	-	1	-	1 (0)
retardation/autism	-	-	-	2	-	2 (0)
anaemia/leukaemia/pancytopenia	-	-	-	4	-	4 (0)
visual disorder	-	-	-	1	-	1 (0)
cerebellar ataxia	-	-	1	-	-	1 (100)
vasculitis	-	-	-	1	-	1 (0)
total 2006	-	11	47	53	-	111(52)

4.9.3 Persistent screaming

In 2006, 61 children with persistent screaming were reported (range 2001-2005 46-133), with positive causality in 93%. Reported persistent screaming appears to be age/dose dependent, as has been noticed in former years (see Table 9). Additional symptoms were pain and swelling at the injection site, restlessness, pallor, myoclonic jerks and fever. 22 Parents gave suppositories, 14 contacted the GP and three children were seen in the hospital (Table 10).

4.9.4 General skin manifestations

In 2006 skin symptoms were the main or only feature in 97 reports. In 2001-2005 this ranged from 73-106. The percentage of reports considered adverse reactions was 62% (range 2001-2005 is 38%-63%). See Table 11 and 19.

Table 19. Skin symptoms and vaccines of reported AEFI in 2006 (adverse reactions)

vaccine⇒ / symptoms⇓	dtp-ipv-hib1	dtp-ipv-hib2	dtp-ipv-hib3	dtp-ipv-hib4	dtp-ipv-hib?	mmr0	mmr1 menc	dt-ipv5 aP	dt-ipv6 mmr2	other	total (AR*)
angio-oedema/swelling	1[a]	-	1	1[a]	-	-	2[b]	-	-	-	5 (4)
exanthema	5[c]	6[c]	1[a]	13[d]	-	2	14	4	6[e]	1[f]	52 (31)
fixed drug reaction	-	-	-	-	-	-	-	1	-	-	1 (1)
urticaria	1[g]	-	3	5[h]	-	-	4	4[i]	1	-	18 (12)
eczema (increase)	5[c]	3[c]	3	-	-	-	2	1	2	-	16 (12)
petechiae /purpura	-	3[c]	-	-	-	-	-	-	-	-	3 (0)
haemangioma	-	1	-	-	-	-	-	-	-	-	1 (0)
dermatitis	1	-	-	-	-	-	-	-	-	-	1 (0)
total 2006	13	13	8	19	-	2	22	10	9	1	97 (60)

* = number of AEFI considered adverse reactions
[a] = with HepB
[b] = once PCV7
[c] = once with PCV7
[d] = five times with HepB
[e] = twice HepB
[f] = HepB
[g] = with HepB and PCV7
[h] = once BCG
[I] = once Influenza

All reports were considered minor events.
Exanthema, (increased) eczema and urticaria were the most frequent events (89%). Five times swelling/angiooedema were reported. Three reported children had petechial rash on upper body and/or face. Children with petechiae on the legs only are categorised under discoloured legs.
31 Cases concerned live attenuated vaccines, 27 times combined with MenC or DT-IPV. In 77% there was a possible causal relation (range 48-77% for 2001-2005). For the inactivated vaccines or combinations, possible causal relation was assessed in 36 out of 66 events, 55% within the range for the five previous years 32-57%. See Table 20.

Table 20. Skin symptoms and causal relation of reported AEFI in 2006

causality⇒ / symptom⇓	certain	probable	possible	improbable	unclassifiable	total (%AR*)
angio-oedema/swelling	-	-	4	1	-	5 (90)
exanthema	-	-	31	21	-	52 (60)
fixed drug reaction	-	-	1	-	-	1 (100)
urticaria	-	-	12	6	-	18 (67)
eczema (increase)	-	-	12	4	-	16 (75)
petechiae /purpura	-	-	-	3	-	3 (0)
haemangioma	-	-	-	1	-	1 (0)
dermatitis	-	-	-	1	-	1 (0)
total 2006	-	-	60	37	-	97 (62)

* percentage of AEFI considered adverse reactions

4.9.5 Discoloured legs

Starting from 1995, discoloured legs are listed in a separate event category, subdivided in blue, red or purple legs with diffuse or patchy discoloration, with or without petechial rash. Leg petechiae without noted discoloration and are also grouped in this category. The same applies for swollen limbs.
In 2006, 124 reports were received, more than twice the number of 2005. (Table 21; range 2001-2004 134-279). There is no trend in increasing numbers of reported discoloured legs during the year, despite the gradual change to an acellular DTP-IPV-Hib vaccine with five pertussis components and the subsequent introduction of PCV7 in the programme for children born since April 2006. 12 Reports were considered to be blue legs (11 double-sided), 60 red legs (27 double sided) and 30 (15 double sided) purple legs. In total, 44 reported leg petechiae, with or without prior discoloration.
In 2005 the share of discoloured legs reported after the first two doses of DTP-IPV-Hib diminished to 53%. In the current year this percentage (77%) returned to levels of 2001-2004 (72-79%). Causal relation with the vaccines was inferred in all but five cases. Only inactivated vaccines were involved. See Table 11.

Table 21. Discoloured legs and vaccines of reported AEFI in 2006

vaccine⇒ symptoms⇓	dtp-ipv-hib1	dtp-ipv-hib2	dtp-ipv-hib3	dtp-ipv-hib4	mmr1 menc	dt-ipv5 aP	dt-ipv6 mmr2	total 2006	2005	2004	2003	2002	2001
blue legs	5[a]	6[f]	1	-	-	-	-	12	5	36	29	26	31
red legs	19[b]	24[d]	8[a]	2[h]	-	7	-	60	26	130	51	40	63
purple legs	13[e]	13[g]	2	2[h]	-	-	-	30	8	69	24	43	56
petechiae only	6[c]	8[c]	2	3	-	-	-	19	15	40	26	23	22
swollen limb	1	-	1	1	-	-	-	3	3	4	4	5	3
total 2006	44	51	14	8	-	7	-	124	57	279	134	137	175

[a] = once with PCV7
[b] = twice with HepB and PCV7, eight times with PCV7
[c] = twice with PCV7 and twice with HepB and PCV7
[d] = once with HepB and PCV7, seven times with PCV7
[e] = once with HepB and PCV7, ten times with PCV7
[f] = four times with PCV7
[g] = six times with PCV7
[h] = once with HepB

4.9.6 Faints

In this event category, collapse (hypotonic-hyporesponsive episode, HHE), syncope (fainting) and breath holding spells (BHS) are listed (Table 22).

Table 22. Faints and vaccines of reported AEFI in 2006

vaccine⇒ event⇓	dtp-ipv-hib1	dtp-ipv-hib2	dtp-ipv-hib3	dtp-ipv-hib4	mmr1 menc	dt-ipv5 aP	dt-ipv6 mmr2	total 2006	2005	2004	2003	2002	2001
collapse	46[a]	21[c]	5[d]	2	1	1[f]		76	75	318	210	270	268
bhs	6[b]	3	-	1	1[e]			11	6	23	9	8	5
fainting	-	-	-	-	1	30[g]	51[h]	82	52	37	25	19	20
total 2006	52	24	5	3	3	31	51	169	133	378	244	297	293

[a] = twice with HepB and PCV7, four times with HepB and 18 times with PCV7
[b] = twice with PCV7
[c] = three times with HepB and PCV7, seven times with PCV7, once DTP-IPV and PCV7
[d] = twice with PCV7
[e] = only MMR
[f] = Influenza
[g] = once DT-IPV only, once PCV7
[h] = once DTP-IPV

In 2006 collapse was reported in 76 cases. This is equal to 2005 but a sharp decrease in numbers compared to 2001-2004. In 61% of cases collapse occurred after the first DTP-IPV-Hib vaccination. In 2005 this was 37%. In 2001-2004 this ranged from 60%-73%. Numbers diminished with dose number and age, similar to 2001-2004. [39,47,50] In 16 reports the event was assessed as not related because of the too long time interval and/or other causes (range 6-16 for 2001-2005). BHS occurred 11 times, of which 73% was causally related to the vaccination; 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 82 times, again an increase compared to the five previous years, in all but one case with assessed causality.

Table 23. Faints and causal relation of reported AEFI 2006

causality⇒ symptom⇓	certain	probable	possible	improbable	unclassifiable	total (%AR*)
collapse	-	56	4	16	-	76 (79)
BHS	-	5	3	3	-	11 (73)
fainting	-	76	5	1	-	82 (99)
total 2006	-	137	12	20	-	169 (88)

* percentage of AEFI considered adverse reactions

Possible causality for reports following MMR was assessed in 51 of the 54 cases (96%). For inactivated vaccines only 97 of the 116 cases (84%) were considered adverse reactions. (Table 23)

4.9.7 Fits

Epileptic seizures and (febrile) convulsions are filed in this category. 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 paragraph 3.5 for case definitions. Most reported convulsions were febrile (57 out of 63), occurring predominantly after the fourth DTP-IPV-Hib (9) and MMR1/MenC (44) vaccinations. For MMR this number is equal to 2005, for DTP-IPV-Hib4 there is a decrease, compared to previous years. In 42 of these the fever was possibly caused by the vaccination and therefore these convulsions were considered adverse reactions. 15 Febrile convulsions were not considered causally related, as there was another cause established and/or an implausible time interval with the vaccination. See also Table 24 and 25.

Table 24. Fits and vaccines of reported AEFI in 2006

event ⇓ vaccine⇒	dtp-ipv-hib1	dtp-ipv-hib2	dtp-ipv-hib3	dtp-ipv-hib4	mmr1 menc	dt-ipv5 aP	dt-ipv6 mmr2	menc	total 2006	2005	2004	2003	2002	2001
febrile convulsion simple	1	-	2	3[a]	24[b]	-	-	-	30	34	45	28	22	26
complex	-	1	-	5[c]	18[d]	-	-	-	24	24	32	23	20	21
tonic	-	-	-	-	-	-	-	-	-	2	5	2	-	2
atypical/not specified	-	-	-	1	2[e]	-	-	-	3	5	8	11	3	2
non febrile convulsion	-	1	2[f]	-	2	1	-	-	6	6	8	6	-	5
epilepsy	-	1[g]	-	-	2[n]	-	-	-	3	4	9	5	5	10
atypical attack	3[i]	3	1[j]	5[k]	7[l]	-	-	-	19	43	104	57	41	55
total 2006	4	6	5	14	55	1	-	-	85	118	211	132	91	121

[a] = once with HepB, once DTP-IPV only
[b] = once MenC only, once MMR only
[c] = once with MMR0, once with HepB
[d] = twice MMR only, once with DTP-IPV-Hib
[e] = once MMR only
[f] = once with HepB
[g] = with PCV7
[h] = once Hib only
[l] = once with PCV7
[j] = BCG
[k] = once with HepB
[l] = once MMR only, once with Yellow Fever and HepA

17 Children had fever ≥ 40.5°C, but these were not listed under major illness since fever was considered part of the event.
Six non-febrile convulsions were reported. Three of these were considered possibly provoked by the vaccination because of correct time interval, the other three were considered chance occurrences.
Three children with epilepsy were reported. In none of these children (fever caused by) the vaccine was regarded as trigger.
In 2006 atypical attacks were recorded 19 times, a decrease compared to previous years. In 10 cases there was a possible causal relation with the vaccination. None of the children fulfilled the case definitions for collapse or convulsion. The reported atypical attacks were

also most frequent after the vaccinations in the one year olds (Table 24). Of the reported atypical attacks 11 were without fever. Three children had fever of $\geq$40.5^{o}C, two times considered causally related to the vaccination.

Table 25. Fits and causal relation of reported AEFI 2006

symptom⇓ causality⇒		certain	probable	possible	improbable	unclassifiable	total (%AR*)
febrile convulsion	simple	-	7	16	7	-	30 (77)
	complex	-	3	13	8	-	24 (67)
	tonic	-	-	-	-	-	-
	atypical	-	-	3	-	-	3 (100)
non febrile convulsion		-	-	3	3	-	6 (50)
epilepsy		-	-	-	3	-	3 (0)
atypical attack		-	4	6	9	-	19 (53)
total 2006		-	14	41	30	-	85 (65)

* percentage of AEFI considered adverse reactions

In 2006 MMR was involved in 54 reports, only five times as a single vaccine. Causality was assumed in 38 cases (70%, range for 2001-2005 is 67-89%). For inactivated vaccines 57% of the reported events were considered adverse reactions (range 2001-2005 37%-71%).

4.9.8 Encephalopathy/encephalitis

The only event reported in 2006 listed in this category was considered a chance occurrence and not induced or aggravated by the vaccination (Table 26).

Table 26. Encephalopathy/encephalitis and vaccines of reported AEFI in 2006

child	sex	age[a]	vaccines	interval	symptoms/diagnosis	causality
A	m	2m	dtp-ipv-hib-hepB +pcv7	1d	seizures, EEG-and MRI-abnormalities, possible mitochondrial disorder	no

4.9.9 Anaphylactic shock

There were no reports on anaphylactic shock in 2006. 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.

4.9.10 Death

In 2006, six children were reported, who died following vaccination (Table 27). The reports concerned five boys and one girl. Autopsy was performed four times, however not in all instances inclusive of full toxicological, microbiologic or metabolic work-up or with post-mortem examination of the brain. Without full post-mortem investigation a definite diagnosis is often impossible. In all six cases death was judged not to be caused or hastened by the vaccination.

Table 27. Death and vaccines of reported AEFI in 2006

child	sex	age[a]	vaccines	time interval illness	time interval death	symptoms/diagnosis	causality	autopsy
A	m	13m	mmr1+menc	3d	4d	congenital abnormalities, metabolic disorder CDG type 1a, fever, seizures, vomiting	no	yes
B	m	4m	dtp-ipv-hib2	1.5-2d	2.5d	crying, pallor,apneu, myo- and endocarditis	no	yes
C	m	2m	dtp-ipv-hib1	-	<24h	congenital heart anomalies, possible arrhythmia, asplenia, SIDS	no	yes
D	f	2m	dtp-ipv-hib1+hepb1	0h	3d	crying, restlessness, no fever, constipation, clinical SIDS	no	no
E	m	16m	mmr1+menc	4w	2.5m	failure to thrive, fever, pneumonia, ARDS	no	no
F	m	2m	dtp-ipv-hib1-hepb1+ pcv7 1	-	1d	SIDS	no	yes

[a] age at vaccination

5 Discussion

The success of the vaccination programme, having brought the target diseases under control, increases the relative importance of side effects. [19,20] 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. [60,61,62] The intensified awareness of the public and professionals with regard to the safety of vaccines may have adverse consequences for the willingness to participate in the programme. It may also influence the number and the type of adverse events following immunisation reported to the safety surveillance system.
We will discuss the characteristics of the current enhanced passive surveillance system and comment on its strength and weaknesses. We will also discuss how the information in the current system may play a role in the management of adverse events and in the risk-benefit communication to professionals and parents.
The Achilles' heel of passive surveillance is underreporting. Especially selective underreporting creates bias. Therefore we will comment upon the representative ness of our data regarding AEFI.

The year under report was given special attention because of the introduction of 7-valent conjugated pneumococcal vaccine (PCV7) administered simultaneously with the DTP-IPV-Hib vaccine for infants born from April first 2006 onwards. The Minister of Health, Welfare and Sport thus followed the advice of the GR of October 2005. [1] We also switched gradually to a DTP-IPV-Hib with five acellular pertussis components.

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.
Below we will go into the increase in number of reports and the different aspects of the nature of the reported adverse events in 2006.
We will discuss the safety of the vaccination programme in the light of the here presented results, with regard to the literature and consider future approaches.

5.1 Number of reports

In 2005 there was a substantial decrease in reports, which was assigned to a DTP-IPV-Hib vaccine with an acellular pertussis component. This is in line with expectation since acellular pertussis vaccines are known to have a more favourable safety profile, both for the more common and the more severe adverse events. [63,64,65] In 2006 the number of reports increased with 12% compared to 2005. The number of multiple and compound reports increased also

compared to 2005, approaching the level before 2004. However, there have always been fluctuations in these numbers, partly depending on degree of follow up.

In the year under report there were several changes in the programme, as mentioned above. However, there was no trend of increasing number of notifications during the year.

5.1.1 Distribution over vaccines and dose

The increase in reports was mainly due to the DTP-IPV-Hib vaccinations. DTP-IPV-Hib reports account for 64% of all reported adverse events, compared to 57% in 2005. In 2001-2004 this ranged from 75% to 81%. There was more predominance (39%) of the first dose compared to 2005 (35%). In 2004 this was 42% and 47% on average in 2000-2003. The first vaccination with DTP-IPV-Hib always has a higher number of reports than the later doses. To some extent this may be due to more concern about the young child and questions about subsequent vaccinations, but the majority is caused by the higher incidence rate of some young-age specific events.
The gradual change to a different composition of the DTP-IPV-Hib vaccine with five instead of three pertussis components might have influenced the number of reports, although a systematic review revealed no difference in safety profile between vaccines with a different number of acellular pertussis components. [66] Usually a safety profile is not based on rare and/or late adverse reactions, which are covered by a passive safety surveillance system. Therefore we can not rule out this change has influenced the number of reported adverse events. However, the introduction of PCV7 hampers a more precise evaluation of this effect. The PCV7 was implemented after the first quarter of 2006, so we expect the share of reports involving a first dose of DTP-IPV-Hib combined with PCV7 to be approximately 50% of the total reports on this dose. Actually this percentage is only 30%. After correction for the fact that part of the birth cohort received two vaccines, the adjusted reporting rate for DTP-IPV-Hib+PCV7 notifications is 2.5/1000 infants (95%CI 2.3-2.7) compared to an unadjusted rate of 3.2. So we can conclude that expanding the RVP with PCV7 doesn't explain the increase in reports.
The number of reports following MMR1 and MenC levelled off. The same applies for the reports following DT-IPV and aP. Until this year reports following these vaccinations showed a repeated annual increase, caused by the introduction of an extra vaccination and reduced underreporting. Ongoing surveillance will show if these numbers will stabilise or change again.
Reports following the vaccinations of the nine-year-olds have increased compared to 2005. See for details the following paragraphs.

5.1.2 Distribution over events

The increase in reports is apparent in nearly all event categories, especially discoloured legs. The number of reported fits, encephalopathy and death did not change. To get more accurate

estimations on the incidence of specific adverse events, we continued the questionnaire study of the more severe adverse events following DTP-IPV-Hib started in December 2003 (to be reported later).
No new or unexpected events were detected in infant age groups in 2006. See for additional information the subparagraphs in 5.2.

5.1.3 Severity, causality, level of intervention and reporting interval

In 2005 the absolute number as well as the relative share of so called major adverse events decreased. This is consistent with the better safety profile of a DTP-IPV-Hib vaccine with an acellular pertussis component. [63,64,65]
This year the relative share of major adverse events increased. Furthermore the percentage of all reports with assessed causality (adverse reactions) increased to 76%, compared to 73% in 2005 (range 2001-2004 is 78-83%). Both the increase in major events and the rise in causality are caused by more reports on acknowledged adverse reactions, like faints and discoloured legs, historically categorised as 'major' events.
In 2005 the percentage of coincidental reports was relatively high, a common phenomenon after introduction of a new vaccine in the schedule. With new vaccines professionals tend to report more events that they formerly would have rejected as obviously not causally related. [39,67] This year the absolute number of reported adverse events with inferred causal relation (282) remained almost the same compared to 2005 (279). Apparently the introduction of pneumococcal vaccine did not cause the same effect.
For the other vaccines or vaccine-combinations the percentage of adverse reactions was similar to previous years.
The level of medical intervention (GP, clinic and hospital visit) was similar to previous years. Relatively fewer children were admitted to hospital in 2006 (9%) compared to 2005 (11%). For both years nearly 70% of these hospitalisations were due to coincidental, unrelated adverse events.

5.1.4 Underreporting

Reducing (selective) underreporting is of special importance in passive surveillance systems. Since 1994 we continuously put extra effort in this, as has been discussed in the previous reports. All repeated annual increases in notifications can be explained by reduced underreporting, introduction of new vaccines or changes in schedule or vaccine composition. [41,42,43,45,48,49,50,51] The reduction of reports in 2005 was caused by the change to an acellular DTP-IPV-Hib vaccine with an acknowledged better safety profile. [63,64,65] Perhaps the expectancy of both public and health clinic workers that this new vaccine "does not have side effects at all" may have strengthened this decrease.
In the current year total number of reports increased significantly, not influenced by the uptake of PCV7, as shown in the previous paragraphs. Possibly the "honeymoon" effect of the acellular DTP-IPV-Hib is fading away. The rather stable even distribution of the reporting

rates over the country and the increase in causality underline this. Perhaps the phased introduction of a DTP-IPV-Hib with five pertussis components may have an additional effect on this rise of reported adverse events.
Continued surveillance is necessary to augment our knowledge on the safety of acellular pertussis vaccine, administered with PCV7 in the Netherlands, The questionnaire study on the more severe, rare events following DTP-IPV-Hib(+PVC7) vaccine is expected to lead to more precise incidence estimates.

5.2 Specific events

In addition to the more general remarks in the above paragraphs some specific adverse events will be discussed below.

5.2.1 Local reactions

Since the introduction of aP at four years of age for the birth cohort 1998 and later the number of local reactions after simultaneous administered DT-IPV and aP increased, most prominently in 2003 and 2005. This year the number of major local reactions following booster dose op DTP-IPV-Hib increased again. Remarkable was the type, extension and the long time interval with vaccination. This may be partly due to decreased underreporting, but is suspect for a true increase in local reactions after pertussis booster vaccinations. [68,69,70] In 2006 we performed a questionnaire study on adverse events after DT-IPV and aP to follow up this signal. Pain, reduced use of the arm, redness, and swelling occurred significantly more often at the DT-IPV injection site than at the aP injection site ($p < 0.05$). Local reactions were mainly mild and transient. [71] We will repeat this study in 2008 with a combined DTP-IPV booster in four-year-olds primed with whole cell pertussis vaccine.

5.2.2 Minor illness

The number of reports in the current year in this category returned to the level before 2004. 212 (53%) of these reports involve fever <40.5^{o}C, crying and pallor. Three quarters (163) concerned DTP-IPV-Hib, equal to the percentage of 2005. For the years 2000-2004 this percentage was approximately 90%. Fever, crying and pallor are acknowledged common adverse events following infant vaccinations. A systematic review in 2003 shows no difference in safety profile between acellular pertussis vaccines with different number of pertussis components. [66] In 33% of the DTP-IPV-Hib reports PCV7 was given simultaneously. This is comparable with the overall percentage of reports, involving PCV7 and lower than expected. (See for more details paragraph 5.1.1) Therefore the addition of PCV7 had no major influence on these numbers.
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. [72] 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. [73,74,75] However comparing these results is hampered by different schedules, vaccine combinations, methods and levels of assessment and lack of uniform case definitions. [64,65,66] Moreover, our passive safety surveillance has a known underreporting for these common adverse events. [76]
Results of the questionnaire study for acellular DTP-IPV-Hib, partly combined with PCV7 are not available yet. We must bear in mind that this annual report does not cover a full year's usage of DTP-IPV-Hib+PCV7.

5.2.3 Very high fever

Fever is an unspecific symptom of many medical conditions. It is also an acknowledged adverse event following immunisation. In all pre registration trials fever is covered. The Brighton Collaboration covered this symptom in the first series of six case definitions with stipulations how to report in increments of .5 degrees centigrade (Celsius). [77] We have registered events under very high fever (≥ 40.5°C) only if the event was not part of another disease entity.
This year 77 events were reported, involving very high fever, of which 29 following DTP-IPV-Hib (four times with PCV7). Compared to 2005 the number of very high fever has increased, but with less emphasis on the one-year-olds (35% and 74% in 2006 and 2005 respectively). In literature difference in fever between DTP-IPV-Hib(+HepB) vaccine with or without PCV7 are described, but variable cut off points of very high fever hamper a good comparison. [72,73,74,75] Longer passive follow up is necessary. More precise estimates will be determined by the current questionnaire survey.

5.2.4 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. There has always been a known underreporting of persistent screaming in the passive surveillance. Exact incidence rates are difficult to compare, because of different case definitions. [78,79,80,81] Moreover it is stated that infants cry on average 2 hours a day during the first months of life, with a peak at 6 weeks with 2.5 hours on average. Our case definition of persistent screaming includes three or more hours continuous crying. This differs from lately redefined Brighton Collaboration case definition, which states "more" than 3 hours crying. [82] We register the duration however in order to be able to pool or compare results.
In literature, estimates of persistent screaming are 1-10 per 1000 children depending on case definition and age involved. [82,83] For the Netherlands we expect results from the current questionnaire study of the acellular pertussis vaccine, whether or not co-administered with PCV7.

5.2.5 Collapse

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. In 2005, one quarter of the reported collapse reactions occurred following whole cell pertussis vaccine, whereas in 2006 all DTP-IPV-Hib vaccines contained an acellular pertussis component. However the number of reported collapse is equal for both years. This may be due to a temporary underreporting of collapse reactions in 2005. Maybe the gradual change to a DTP-IPV-Hib vaccine with five pertussis components had some influence, but the introduction of PCV7 hampers a more precise evaluation of this effect.
Collapse reactions occurred most frequently after the first and second dose (88%). In 2006 47% of these reports concerned DTP-IPV-Hib simultaneously administered with PCV7. This is higher than the average this year (30%).
Ongoing surveillance is necessary to gain insight in incidence rates for collapse following DTP-IPV-Hib combined with PCV7 vaccine. A questionnaire study on rare severe adverse events following whole cell DTP-IPV-Hib showed a good performance of the enhanced passive surveillance system for more complex events like collapse. In the near future we will look into collapse reactions, reported to the enhanced passive surveillance system in relation to acellular pertussis vaccines more carefully.

5.2.6 Discoloured legs

Numbers of reported discoloured legs have more than doubled compared to previous year. In 2005 77% of the reports followed DTP-IPV-Hib, all but six with an acellular pertussis component. In the current year 94% of the reports occurred after DTP-IPV-Hib, in 42% simultaneously administered with PCV7. Again this percentage is higher compared to all reports on average (30%).
The increase may be an indication of reduced underreporting of discoloured legs following acellular pertussis vaccines. Maybe the phased introduction of DTP-IPV-Hib with five pertussis components played a role. Perhaps it is also influenced by the concomitant PCV7 vaccination, although there is no trend in increasing numbers of discoloured legs during the year. We have to bear in mind that this report does not cover a full year use of PCV7.
Ongoing surveillance is necessary to gather more accurate numbers on this subject.

5.2.7 Convulsions and atypical attacks

The number of (classic) febrile convulsions was considerably lower than in previous years. Most reported febrile convulsions occur in the one-year-olds. The number following MMR and MenC is equal to 2005, for DTP-IPV-Hib4 the number is lower. This maybe caused by the lower rate of fever following acellular pertussis vaccines. [63,64,65] After a full year use of acellular pertussis vaccine the incidence rate, irrespective of assessed causality, for DTP-IPV-Hib4 is 0.5 (95% CI 0.2-0.8) per 10,000 vaccinations. This is lower than previous estimates

following whole cell pertussis vaccine. [84,85] In the following years with only acellular pertussis vaccine in use, the performance of the acellular pertussis vaccine will become manifest.
The number of reported atypical attacks was substantially lower than the five previous years. Numbers fluctuate however. This is not surprising if one considers this subcategory to be the dustbin of paroxysmal events not otherwise classifiable. We follow the reports in this subgroup with scrutiny but up till now no specific trends or signals were observed. The numbers in this subgroup are (very much) dependent on completeness of information. Thus, transfer to and from other event categories in different years.

5.2.8 Pervasive disorders and retardation

Press allegations about possible causal relation between MMR vaccination and autism dented the confidence of parents in the vaccination programme. [86,87] Despite the fact that based on scientific evidence renowned (groups of) scientists have refuted these alleged associations, the vaccination coverage dropped considerably, especially in the United Kingdom and the Republic of Ireland. [88,89] In the current year we have received very few reports on behavioural problems in the autistic spectrum or other specific problems in mental retardation. Some parents have no real suspicion but have been made insecure; others simply clutch the last straw. In none of the reported cases a causal relation was found, and in some the event preceded the vaccination.
It is to be expected that the number of reports of events that have attracted public attention will increase. A passive surveillance system, even an enhanced one, is not the proper tool for a refutation of false hypotheses, or for substantiating true ones for that matter. Recently a few systematic studies have been published showing no causal relation of disturbances in the autistic spectrum with MMR vaccination or thiomersal containing pertussis vaccine. [90,91]
Studies refuting the causal relation of encephalopathy or retardation with pertussis vaccinations have been published earlier and confirmed lately. [92]
In fact, in Australia 11 of 14 children with alleged vaccine encephalopathy appeared to have a SCN1A mutation. [93] This mutation is associated with Severe Myoclonic epilepsy in infancy (SMEI). Most mutations are “de novo” and not inherited. In collaboration with the section for genetic counseling of the UMC Utrecht, we will investigate all reported complex febrile convulsions, epilepsy or pervasive disorders of the years 1997-2006 to see if this mutation plays a role.

5.2.9 Epilepsy

The number of reports on epilepsy was within the range of the last five years, with comparatively a rather large variation, as is to be expected with such small numbers. In none of the reports causality was assumed. Current scientific data do not support any causal relation between epilepsy and vaccinations. In the past years a number of studies have been performed on the aetiology of epilepsies. [83] However, it may not be possible to exclude this

causal relation definitely in an individual case. Vaccines may cause convulsions, mainly indirectly through fever, in prone children. As for West syndrome, epidemiological evidence refutes a causal relation. [94] However, the age at which West syndrome occurs coincides with the vaccination schedule.

5.2.10 Death

This year six children were reported who died some time after immunisations. The number of reports in this category is in line with expectations considering the background rate. After thorough evaluation in none of the children causality with the vaccinations was assessed. 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. [95] In an individual case, this may not be demonstrated easily. Especially in the case of possible SIDS this poses a problem. Diagnosis of SIDS is possible only after extensive post-mortem examination has not revealed a cause of death. Therefore it is of utmost importance to insist on full post-mortem investigations and to report fully on all infant deaths following vaccinations. Even if causation is very remote, it is known that in the direct vicinity of the case there is an adverse effect on compliance to the programme, of public and professionals. It should be emphasised that death in close time relationship, i.e. for inactivated vaccines within one month and for live vaccines within six weeks, should be reported in all instances, regardless of cause. Sooner or later someone will question the effect of the vaccinations even if on first sight causal relation seems to be remote. It is better to be pro-active than to have to follow up on (public) disquiet. If parents are not aware of notification, reporting anonymously is the better choice than to postpone until parents are consulted. Explanation to parents that assessment of the involvement of prior vaccination is performed routinely, and not only if there is suspected contribution of the vaccination to the death, will satisfy most parents.

5.3 Safety surveillance of the RVP

Safety surveillance of the vaccination programme seems to be of increasing importance. [19,20,96,97,98] The Dutch system has several strong points. Denominators are known, because the PEA registers all administered vaccines on individual level. [4,5,10] The installation of the web-based new central vaccination register will allow more specific and timely data extracting (Praeventis). The data warehouse tool will make data extraction more efficient (Praemis). 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 the next dose. The RIVM's central telephone information and consultation service for professionals is an important and efficient tool in adverse events reporting. [99] 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 nominal reports facilitate follow up and some other systematic studies, like nested case-control studies. [49,100] The current enhanced passive surveillance system performs satisfactory (LIBRIS). The strength of the system outweighs the inherent weaknesses. Additional active surveillance studies should supplement the passive system.
See for further details the subparagraphs below.

5.3.1 Causality assessment and case definitions

Assessing causal relation is essential in monitoring the safety of the vaccination programme. [101,102,103,104] Of course, after vaccination does not mean caused by vaccination. The RIVM expert panel has continued the former GR activities of broader scientific assessment of selected cases with complete agreement on diagnosis and causality. Some other countries have followed suit, like Canada (with its ACCA, Advisory Committee on Causality Assessment, since 1994), the USA (CISA, Clinical Immunization Safety Assessment Centres, since 2001) and Australia.[105,106,107] 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. [108] Also different schedules and/or vaccines and combinations do preclude direct analyses 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 adverse events following immunisations. Use of these case definitions is proposed for both pre-licensure studies and post-registration surveillance. [16,104] Performance of vaccines in comparative pre-registration field trials may differ from experiences in actual use in large unselected populations. Therefore (new) vaccines should be monitored intensely and exactly, when they are in actual use.

5.3.2 Passive surveillance versus active surveillance

The current enhanced passive surveillance system need to be supplemented by more active monitoring and systematic studies to test generated signals and hypotheses. Problems arising from privacy legislation should be addressed. The introduction of a unique medical personal identifier should facilitate data linkage studies, using hospital databases or other electronic medical files. The centralised vaccination register is an asset towards these goals.
With the possible uptake of new vaccines at different age-groups, there is a growing need for monitoring adverse events, especially auto-immune disorders. [109] 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. We will study the possibilities of such a monitoring system in the near future.
The enhanced passive surveillance however, will remain the backbone of safety surveillance. In an EU study in several European countries, including the Netherlands, possibilities for improved safety surveillance of vaccination have been explored (EUsafevac 2001-2003). [110,111,112] Different Health Care systems and vaccine delivery organisations and logistics, with different legislation, traditions, among other things, but also existing differences in safety surveillance already in place, make that no unique recommendation could be made. Stressed is however that vaccination registers are a first requisite. [113] These registers should also qualify for safety surveillance. In the Netherlands the new centralised vaccination database fulfils these criteria; vaccination registers existed since the early seventies.
In Canada the national safety surveillance system is placed at the Public Health Agency of Canada (CAEFISS) to ensure that vaccine safety surveillance with its specific aspects, is guaranteed. They have an active surveillance system in place for severe adverse events following immunisation, vaccine failure and (future) vaccine preventable infections (IMPACT, a collaboration of the Canadian Paediatric Society and the Centre for Infectious Diseases). In the USA vaccine safety surveillance is also separate from the drug monitoring system situated at the CDC in collaboration with FDA (VAERS). The vaccine safety data link project (VSD) links immunisation record with medical information in the database of some large Health Maintenance Organisations (HMO) to perform active studies testing signals from the passive system. In the Netherlands the placement of the safety surveillance system at RIVM (LIBRIS) with its expertise should guarantee high quality assessment of the safety of the RVP. The collaboration with Lareb should ensure that European legislation is followed.
In the Netherlands the feasibility of using the Paediatric Surveillance Unit for active signal testing for specific adverse events has been explored, but more continuous collaboration should be undertaken. The performance of the system and the degree of participation and coverage should be guaranteed however. Possibilities of electronic databases of paediatric diagnoses should be explored. For the more severe common adverse events questionnaire survey could be done on a regular basis to test the safety profile of the (new) vaccines or schedules in the programme. For the more rare complex adverse events questionnaire surveys appear to be less suitable. Perhaps targeting certain selected adverse events at the clinic will give a better yield.

5.3.3 Information and consultation service

We hold the telephone service to be an important tool in the safety surveillance of the RVP, both for capture of important adverse events or potential adverse reactions and with regard to the quality of data. [114] This low threshold reporting channel has proven to have great advantage over written report forms not only because of superior possibility of communication, timeliness and supplementation of data. Written reports by regular mail, by fax and by e-mail are also accepted. The telephone service is also an important tool for

adherence to the programme, to promote proper use of contraindications and for guidance of the professionals to ensure adequate vaccination in special circumstances or underlying disorders.
There is a growing public demand for more and better information, both for general questions and for child specific problems. More readily available and accessible printed general and specific information is needed, also for professionals. [115,116,117,118,119] The RVP communication project of RIVM in close collaboration with other parties has developed fact sheets and web based material for parents in spring 2004. It is planned to add more in depth material for professionals. (www.rvp.nl)
Feedback of the summarised annual reports on the safety of the vaccination programme should be ready in a more accessible and timely manner both for professionals and public.
See also the following paragraphs on management of adverse events and risk communication.

5.4 Management of adverse events

The increasing relative importance of potential side effects makes careful surveillance of the safety of the vaccination programme even more important than before. Just signal detection isn't enough. Evaluation and feedback communication should complement mere registration. Signals should be followed up with more systematic studies. Information about reported adverse events should have a place within the risk communication to parents. Some side effects are unavoidable, but where possible the aim should be to prevent adverse reactions. Adverse coincidental events are truly chance occurrences however. Sometimes postponement of vaccination might free the vaccine and the vaccination programme from allegations of causing an event or disorder that would inevitably have occurred. But deferral should be avoided as much as possible because it will delay protection of the child.

5.4.1 Prevention and treatment of adverse events

Adverse reactions or side effects do occur and parents should know what to expect. They need instruction about what (not) to do to alleviate symptoms. In the communication about the risk of vaccination, attention should be paid to the decrease in (awareness of the risk of) occurring target diseases. It should however also be stressed that not everything occurring after a vaccination is indeed caused by the vaccine. One of the most severe adverse events is undue, even fatal delay in recognising severe coincidental illness, because symptoms are wrongfully attributed to the vaccine. [39,40,41,42,43,45,46,48,49,50] Some education of the professionals in this respect seems warranted also. The vaccination as cause should be in the differential diagnosis, nothing less but at the same time nothing more.
Proper procedures and techniques are important in minimising adverse reactions and the proper use of paracetamol should be included in the information to parents.

5.4.2 Contraindications

Contraindications for the RVP vaccines have been abandoned more or less completely. [3,120,121,122,123] Proper application of true contraindications should be adhered to however to prevent undue side effects. But false contraindications should be avoided on the other hand because they lead to missed opportunities to provide protection. Applying more strict contraindications will not contribute much to prevention of adverse reactions but will result in a loss of protection. [124]

5.4.3 Risk communication

The telephone information service and the adverse event surveillance system have made us increasingly aware of the need of (at least a group of) parents for more balanced and readily accessible information about the pro's and con's of the vaccination programme. More and more providers signal the need for more apt and specific information to be communicated (by them) to parents. The providers may be the best-informed professionals in vaccination matters but they also need timely information for their own reflections. They do need up-to-date facts and figures. Providers and parents should be systematically informed about the risk-benefit balance of the programme. The successful control of the target diseases has diminished awareness of the severity of the target diseases and increased the perceived risk of complications and sequelae. Child Health Care personnel should be equipped with more direct, adequate, up to date information on matters of vaccine safety. The present anti-vaccine-movements and the confusion they create make this argument more compelling. The Minister of Health has recognised the need for this repeatedly and answered as much to questions by members of the parliament repeatedly. Halfway 2003 the necessary funds have been allocated to RIVM and since then a special project for improved and enhanced education and communication has been underway, in close collaboration with providers and PEA. This comprises web-based information, fact sheets on different topics of the RVP, newsletters and comprehensive training material. Needless to say this cannot be available all at the same time. Since information needs to be updated and new needs arise, this requires a continuous project, in order to reach the goals. From January 2004 information is available on www.rivm.nl and since April 2004 on www.rvp.nl.
The experiences in 2004 with extreme public media concern about the safety of the vaccines have indeed accentuated the need for timely up to date information. Especially professionals have stressed that they should be informed proactively, not only by news letters but also through specific scientifically referenced fact sheets.

5.4.4 Causality assessment

Causality assessment is important for surveillance purposes of the vaccines, the vaccination programme and for the individuals concerned. [101,102,103,104] Individual continuation of the schedule depends on proper assessment. It is important for the entire population served, as both in quietude and commotion will result in diminished coverage. One should acknowledge

genuine adverse reactions and recognise evidently coincidental events both. Careful causality assessment will exonerate the programme from severe but unrelated adverse events. It will also detect new rare adverse reactions and as yet new unrecognised more common side effects. Therefore thorough causality assessment will enhance the safety of the programme.

5.5 Considerations for the safety surveillance of the RVP

In 2006 we implemented a DTP-IPV-Hib vaccine with five pertussis components for infants and added the conjugated pneumococcal vaccine to the programme. The year under report showed an increase of (causal related) reported adverse events, not explained by the introduction of the PCV7. Perhaps the phased introduction of DTP-IPV-Hib with five pertussis components has influenced this rise. However aanalysis of this effect is hampered by the introduction of the PCV7 in the second quarter of 2006. Probably reduced underreporting is a good explanation for the increase in reported AEFI.
Passive safety surveillance in the next years will reveal the safety profile of this combination in more detail. However frequent changes in product and additions to the schedule may impede comparisons. For some adverse events the results of the questionnaire study will supply incidence estimates.
It's worth to increase the reach of the system not only among the current providers, but especially among pediatricians. This may yield more reports but this also should result in more timely reports. Depending on type of event, supplementation of the system with active surveillance through parental questionnaires or pediatric surveys is necessary.
Possibilities of data linkage must be explored. Shortcomings like undue privacy concerns and the absence of outcome databases or common personal identifiers that may be used for data linkage purposes should be addressed. Without the use of these new epidemiological designs that may expand our knowledge of adverse events may be hampered. Medical data must be validated and must contain sufficient information to apply (internationally) agreed case definitions.
An adequate database system is a prerequisite for this as well. The data put into the system must be of good quality nevertheless; therefore this should get a lot of attention. "Rubbish in rubbish out" also applies to safety surveillance.
Structural feedback to reporters and otherwise involved professionals should be addressed in the new database application. This also serves (expedited) passing on of reports to Lareb and manufacturers.
We acknowledge the need for timely and up to date safety information. Results from the surveillance system and the inference and implications should be available in comprehensive format, both for professionals as for public. The system should also decisively address adverse publicity and other signals. We plan to produce proactively scientifically based fact sheets on severe and rare events that may counteract unfounded future allegations. Those fact sheets will help the professionals to deal with correct or inappropriate contraindications.

6 Conclusions and recommendations

In 2006 the number of reported events increased significantly. The addition of conjugate pneumococcal vaccine from April 2006 onwards had little influence on this rise. The possible effect of the change to a DTP-IPV-Hib with five pertussis components is hard to establish, due to the gradual implementation, followed directly by the introduction of PCV7. Data on 2007 will give more insight in the simultaneous administration of these two vaccines.
Continuous safety surveillance is an essential part of the vaccination programme. The passive safety surveillance will remain the backbone and where appropriate will be supplemented by more systematic studies. Feedback to professionals and public is necessary.
Incidence rates of more common events like fever and crying are expected from the questionnaire study. For the more rare collapse and convulsion the enhanced passive surveillance system performs satisfactorily, as was shown by the questionnaire study of 2004.
For rare severe events special study designs are needed to assess causal relation with the vaccination. Results sometimes may confirm suspected causal relation and other times refute allegations.
The new adopted database system for adverse event surveillance will allow further detailed aggregated analysis of the reports and also facilitate systematic feed back to the reporters as well as data exchange with other bodies, nationally and internationally. Safety surveillance systems in the future should be prepared to study generated signals of specific rare or long-term adverse effects on short notice. 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. [109,125,126]
Introduction of new vaccines should be organised in a way that allows safety studies on the long term also. 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 perform needed specific studies and increase scientific knowledge about adverse events following vaccinations. Eventually this will boost public confidence in the programmes.
For the coming year, if resources permit, the next topics are recommended:

- further implementation of database applications and mutual adjustment with Lareb;
- annual report on 2007;
- maintenance and evaluation of the current passive surveillance system;
- further increasing reporting compliance of child health care providers;
- promoting safety surveillance and information system among paediatricians;
- second case control study on follow up of collapse reactions;
- exploration of possibilities of data linkage or sentinel studies, to test generated hypotheses;
- study on vaccinations and SIDS;

- study on epilepsy/retardation and SMEI;
- study on adverse events following DTP-IPV/HIB and pneumococcal vaccinations of preterm infants;
- active follow up of changes in the programme.

The total of 1159 reports must be seen in relation to a total of over 1.4 million vaccination dates administered with nearly 7 million components. We showed that the vaccination programme is safe with the potential side effects far less in weight than the apparent achievements/prevented illness and complications. We plan to keep up a thorough high quality safety-surveillance-system and to stimulate reporting in the coming year.

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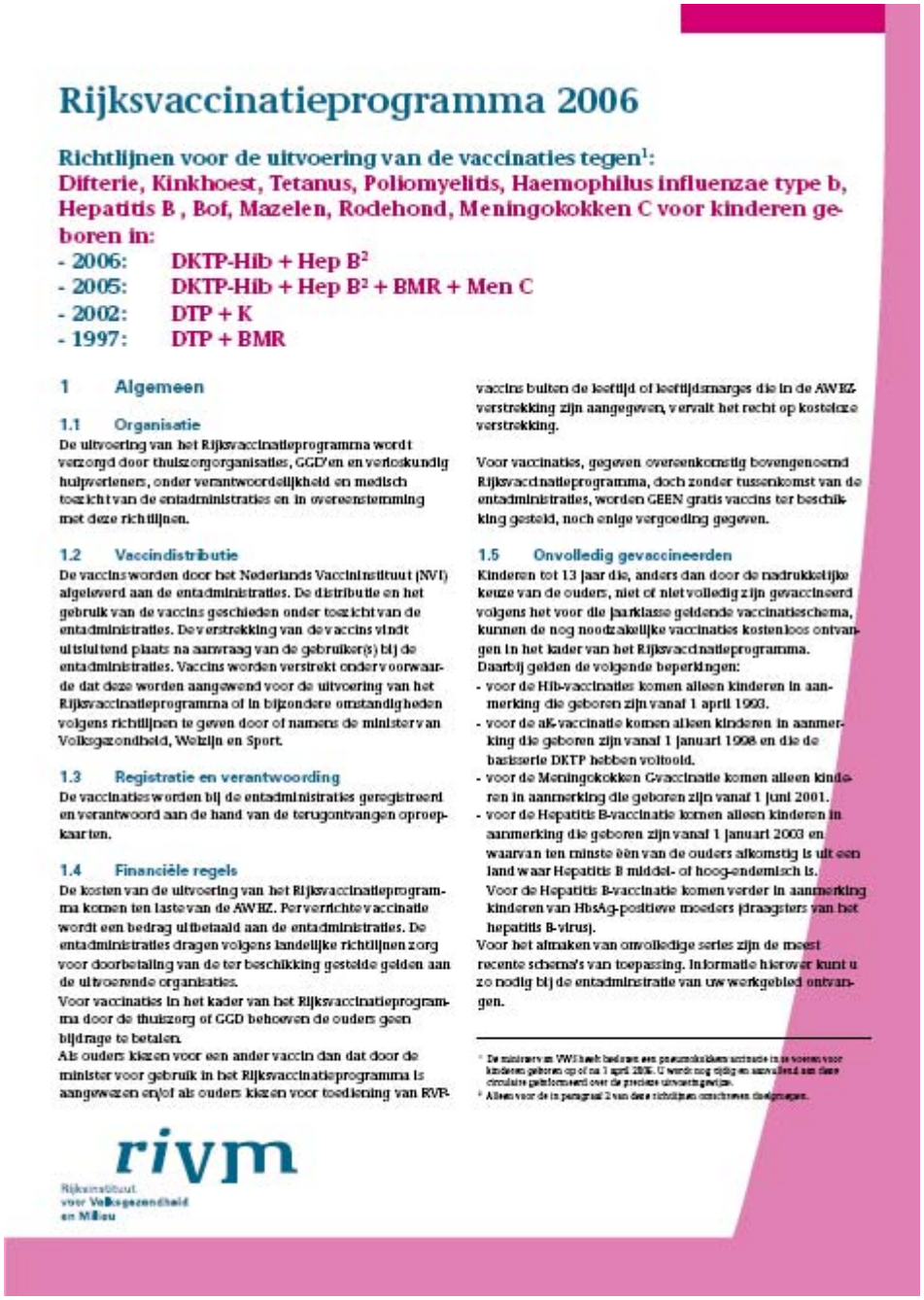
Appendix 1 Vaccination Programme 2006



Rijksvaccinatieprogramma 2006

Richtlijnen voor de uitvoering van de vaccinaties tegen[1]:
Difterie, Kinkhoest, Tetanus, Poliomyelitis, Haemophilus influenzae type b, Hepatitis B , Bof, Mazelen, Rodehond, Meningokokken C voor kinderen geboren in:

- 2006: DKTP-Hib + Hep B[2]
- 2005: DKTP-Hib + Hep B[2] + BMR + Men C
- 2002: DTP + K
- 1997: DTP + BMR

1 Algemeen

1.1 Organisatie

De uitvoering van het Rijksvaccinatieprogramma wordt verzorgd door thuiszorgorganisaties, GGD'en en verloskundig hulpverleners, onder verantwoordelijkheid en medisch toezicht van de entadministraties en in overeenstemming met deze richtlijnen.

1.2 Vaccindistributie

De vaccins worden door het Nederlands Vaccininstituut (NVI) afgeleverd aan de entadministraties. De distributie en het gebruik van de vaccins geschieden onder toezicht van de entadministraties. De verstrekking van de vaccins vindt uitsluitend plaats na aanvraag van de gebruiker(s) bij de entadministraties. Vaccins worden verstrekt onder voorwaarde dat deze worden aangewend voor de uitvoering van het Rijksvaccinatieprogramma of in bijzondere omstandigheden volgens richtlijnen te geven door of namens de minister van Volksgezondheid, Welzijn en Sport.

1.3 Registratie en verantwoording

De vaccinaties worden bij de entadministraties geregistreerd en verantwoord aan de hand van de terugontvangen oproepkaarten.

1.4 Financiële regels

De kosten van de uitvoering van het Rijksvaccinatieprogramma komen ten laste van de AWBZ. Per verrichte vaccinatie wordt een bedrag uitbetaald aan de entadministraties. De entadministraties dragen volgens landelijke richtlijnen zorg voor doorbetaling van de ter beschikking gestelde gelden aan de uitvoerende organisaties.
Voor vaccinaties in het kader van het Rijksvaccinatieprogramma door de thuiszorg of GGD behoeven de ouders geen bijdrage te betalen.
Als ouders kiezen voor een ander vaccin dan dat door de minister voor gebruik in het Rijksvaccinatieprogramma is aangewezen en/of als ouders kiezen voor toediening van RVP-vaccins buiten de leeftijd of leeftijdsmarges die in de AWBZ-verstrekking zijn aangegeven, vervalt het recht op kosteloze verstrekking.

Voor vaccinaties, gegeven overeenkomstig bovengenoemd Rijksvaccinatieprogramma, doch zonder tussenkomst van de entadministraties, worden GEEN gratis vaccins ter beschikking gesteld, noch enige vergoeding gegeven.

1.5 Onvolledig gevaccineerden

Kinderen tot 13 jaar die, anders dan door de nadrukkelijke keuze van de ouders, niet of niet volledig zijn gevaccineerd volgens het voor die jaarklasse geldende vaccinatieschema, kunnen de nog noodzakelijke vaccinaties kosteloos ontvangen in het kader van het Rijksvaccinatieprogramma.
Daarbij gelden de volgende beperkingen:

- voor de Hib-vaccinaties komen alleen kinderen in aanmerking die geboren zijn vanaf 1 april 1993.
- voor de aK-vaccinatie komen alleen kinderen in aanmerking die geboren zijn vanaf 1 januari 1998 en die de basisserie DKTP hebben voltooid.
- voor de Meningokokken C-vaccinatie komen alleen kinderen in aanmerking die geboren zijn vanaf 1 juni 2001.
- voor de Hepatitis B-vaccinatie komen alleen kinderen in aanmerking die geboren zijn vanaf 1 januari 2003 en waarvan ten minste één van de ouders afkomstig is uit een land waar Hepatitis B middel- of hoog-endemisch is.
  Voor de Hepatitis B-vaccinatie komen verder in aanmerking kinderen van HbsAg-positieve moeders (draagsters van het hepatitis B-virus).

Voor het afmaken van onvolledige series zijn de meest recente schema's van toepassing. Informatie hierover kunt u zo nodig bij de entadministratie van uw werkgebied ontvangen.

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[1] De minister van VWS heeft besloten een pneumokokken vaccinatie in te voeren voor kinderen geboren op of na 1 april 2006. U wordt nog nader en aanvullend aan deze circulaire geïnformeerd over de precieze uitvoeringswijze.
[2] Alleen voor de in paragraaf 2 van deze richtlijnen omschreven doelgroepen.

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1.6 Algemene regels ten aanzien van het toedienen van de vaccins

Het toedienen van RVP-vaccins is een medische handeling. Voor het wel of niet toedienen hiervan en voor het afwijken van de in het schema aangegeven leeftijdsmomenten (zie paragraaf 7) geldt derhalve, dat hiertoe altijd door een arts een indicatie moet zijn gesteld.

Voor alle vaccins in het kader van het Rijksvaccinatieprogramma geldt dat halvering van de dosering van een vaccin niet is toegestaan. Het effect hiervan op de werkzaamheid is namelijk onbekend, terwijl het niet leidt tot minder bijwerkingen. Ook andere afwijkende doseringen of verdunningen van de vaccins zijn niet toegestaan.

Verder geldt voor alle vaccins, dat deze niet intravasculair toegediend mogen worden.

1.7 Nadere regelingen

Alle systematische afwijkingen met betrekking tot de uitvoeringsvoorschriften van het Rijksvaccinatieprogramma 2006 vereisen de goedkeuring van de directeur van het Centrum Infectieziektebestrijding.

1.8 Extra circulaires

Exemplaren van deze circulaire kunt u aanvragen bij uw regionale entadministratie (zie paragraaf 8). De circulaire is ook te vinden op www.rvp.nl.

2 Zuigelingen

Vaccinatieschema

DKTP (Difterie – Kinkhoest - Tetanus - Poliomyelitis) - Hib (Haemophilus influenzae type b)

Op de leeftijd van respectievelijk 2, 3 en 4 maanden wordt één DKTP-Hib-vaccinatie gegeven. Er dient minimaal een periode van 4 weken in acht te worden genomen tussen de drie opeenvolgende vaccinaties. De vierde DKTP-Hib-vaccinatie wordt bij voorkeur gegeven op de leeftijd van 11 maanden. Er dient tenminste een tussenperiode van 6 maanden in acht te worden genomen tussen de derde DKTP-Hib-vaccinatie en de vierde DKTP-Hib-vaccinatie. Voor de wijze van menging wordt naar de bijsluiter verwezen. Dosering: 0,5 ml INTRAMUSCULAIR.

In het kader van het RVP dient in principe altijd gemengd DKTP-Hib-vaccin toegediend te worden. Separaat toedienen van Hib-vaccin is alleen toegestaan in het kader van het RVP aan kinderen die op latere leeftijd Nederland binnenkomen en die in aanmerking komen voor Hib-vaccinatie, maar niet (meer) voor DKTP-Hib-vaccinatie. Vanaf de leeftijd van 1 jaar kan dan met één Hib-vaccinatie worden volstaan. Indien kinderen nog in aanmerking komen voor een DKTP-vaccinatie maar niet meer voor een Hib-vaccinatie, kan in het kader van het RVP alleen DKTP-vaccin toegediend worden.
DTP-vaccin en Hib-vaccin mogen **nooit** gemengd worden.

Hep B (Hepatitis B)

Voor deze vaccinatie komen uitsluitend twee groepen kinderen in aanmerking:

1. Kinderen waarvan ten minste één van de ouders afkomstig is uit een land waar Hepatitis B middel- of hoog-endemisch is (prevalentie van dragerschap ≥ 2%)[1].
2. Kinderen van HbsAg-positieve moeders (draagsters van het Hepatitis B-virus).

Ad 1) Kinderen waarvan ten minste één van de ouders afkomstig is uit een land waar Hepatitis B middel- of hoog-endemisch is (prevalentie van dragerschap ≥ 2%).
Aan deze kinderen wordt op de leeftijd van 2 en 4 maanden één Hep B-vaccinatie gegeven. De **derde** Hep B-vaccinatie wordt bij voorkeur op de leeftijd van 11 maanden gegeven. Er dient **tenminste een tussenperiode van 6 maanden** in acht te worden genomen tussen de tweede Hep B-vaccinatie en de derde Hep B-vaccinatie.
Dosering: 0,5 ml INTRAMUSCULAIR.

De Hep B-vaccinatie wordt simultaan (op dezelfde dag) met de DKTP-Hib-vaccinatie gegeven, waarbij het Hep B-vaccin en het DKTP-Hib-vaccin in verschillende ledematen worden toegediend.

Ad 2) Kinderen van HbsAg-positieve moeders (draagsters van het Hepatitis B-virus).
Aan deze kinderen wordt op de leeftijd van 0, 2, 4 en 11 maanden een vaccinatie gegeven. De eerste Hep B-vaccinatie op t=0 wordt uitgevoerd door de verloskundig hulpverlener en dient in principe te worden toegediend binnen 48 uur na de geboorte van het kind, liefst direct na het toedienen van het hepatitis B-immunoglobuline. Indien dit bij uitzondering niet mogelijk is, dient de vaccinatie in elk geval binnen uiterlijk 1 week toegediend te zijn. Het vaccin dat in een dosis van 0,5 ml intramusculair moet worden gegeven (in een ander beentje dan waarin het immunoglobuline is toegediend), zal door de entadministratie in uw regio worden verstrekt.
Vanaf 2 maanden wordt de serie Hep B-vaccinaties bij deze kinderen afgemaakt volgens het schema en de richtlijnen zoals vermeld onder ad 1). Omdat het hier post-expositie profylaxe betreft en geen preventie, dient het schema van 0, 2, 4 en 11 maanden strikt gevolgd te worden.
Uitstel van de Hep B-vaccinatie is dus niet toegestaan voor kinderen met een moeder die draagster is van het Hepatitis B-virus (HbsAg-positief) om te voorkomen dat het kind besmet raakt en zelf ook drager wordt. Deze vaccinatie zal landelijk worden ingevoerd op 1 januari 2006. U bent hierover reeds separaat geïnformeerd in november/december 2005 door middel van een aanvullende IGZ-circulaire (kenmerk 2005-7-IGZ).

BMR (Bof - Mazelen - Rodehond)

Op de leeftijd van 14 maanden wordt één BMR-vaccinatie gegeven.
Dosering: 0,5 ml SUBCUTAAN.

[1] De WHO geeft een lijst van landen waar hepatitis B laag-endemisch is, de zogenaamde negatieve landenlijst: Andorra, Australië, Bahamas, Barbados, België, Bermuda, Canada, Chili, Colombia, Costa Rica, Cuba, Cyprus, Denemarken, Duitsland, El Salvador, Finland, Frankrijk, Hongarije, Ierland, Luxemburg, Malta, Monaco, Nederland, Nicaragua, Nieuw-Zeeland, Noorwegen, Oostenrijk, Paraguay, Peru, San Marino, Sri Lanka, Slowakije, Tsjechië, Uruguay, Qatar, Verenigd Koninkrijk, Verenigde Staten, Zweden en Zwitserland.

Men C (Meningokokken C)
Op de leeftijd van 14 maanden wordt één Men C-vaccinatie gegeven.
Dosering : 0,5 ml INTRAMUSCULAIR.
De Men C-vaccinatie wordt simultaan (op dezelfde dag) met de BMR-vaccinatie gegeven, waarbij het Men C-vaccin en het BMR-vaccin in verschillende ledematen worden toegediend.

3 Kleuters

Vaccinatieschema

DTP (Difterie - Tetanus - Poliomyelitis)
De in 2002 geboren kinderen worden in 2006 gevaccineerd met DTP-vaccin.
Dosering: 1 ml INTRAMUSCULAIR.

(Kinkhoest)
De in 2002 geboren kinderen worden in 2006 gevaccineerd met aK-vaccin, maar uitsluitend indien zij al eerder een volledige serie DKTP-vaccinaties hebben ontvangen. Er wordt één aK-vaccinatie gegeven.
Dosering: 0,5 ml INTRAMUSCULAIR.

Als kinderen geen (volledige) serie DKTP-vaccinaties hebben ontvangen, dient deze serie met DKTP(-Hib)-vaccin en niet met los DTP- en aK-vaccin afgemaakt te worden, vanwege de hogere sterkte van enkele componenten in het DKTP-vaccin. DKTP(-Hib)-vaccin wordt tot de leeftijd van 5 jaar (60 maanden) aangeboden.

De aK-vaccinatie wordt simultaan (op dezelfde dag) met de DTP-vaccinatie gegeven, waarbij het aK-vaccin en het DTP-vaccin in verschillende ledematen worden toegediend.
Kinderen ouder dan 6 jaar (72 maanden) mogen geen aK-vaccin meer ontvangen; het vaccin is hiervoor niet geregistreerd.

4 Schoolkinderen

Vaccinatieschema

DTP (Difterie - Tetanus - Poliomyelitis)
De in 1997 geboren kinderen worden in 2006 gevaccineerd met DTP-vaccin.
Dosering: 1 ml INTRAMUSCULAIR.

BMR (Bof - Mazelen - Rodehond)
De in 1997 geboren kinderen krijgen in 2006 een BMR-vaccinatie.
Dosering: 0,5 ml SUBCUTAAN.

De BMR-vaccinatie wordt simultaan (op dezelfde dag) met de DTP-vaccinatie gegeven, waarbij het BMR-vaccin en het DTP-vaccin in verschillende ledematen worden toegediend.

5 Simultane vaccinaties en registratie van partijnummers

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

Als deze vaccinaties om een of andere reden niet simultaan kunnen worden gegeven, dienen tussen de vaccinaties de volgende intervallen aangehouden te worden:
- Na toedienen van een dood vaccin, zoals een DKTP(-Hib)-vaccinatie, een DTP-vaccinatie, een Hib-vaccinatie, een Hep B-vaccinatie, een Men C-vaccinatie of een aK-vaccinatie, dient 2 weken gewacht te worden alvorens een ander vaccin mag worden toegediend.
- Na toedienen van een levend verzwakt vaccin, zoals een BMR-vaccinatie, dient 4 weken gewacht te worden alvorens een ander vaccin mag worden toegediend.
  Uitzondering hierop vormt de BCG-vaccinatie (tegen TBC); voor en na deze vaccinatie hoeft geen interval aangehouden te worden.

Er dient per gevaccineerde zuigeling, kleuter en schoolkind bekend te zijn in welke ledematen de DKTP-, Hib- (al dan niet gecombineerd), Hep B-, Men C-, BMR-, DTP- of aK-vaccinaties zijn toegediend in verband met de herkenning van (mogelijke) lokale bijwerkingen. Daarnaast dienen ook de partijnummers van het toegediende vaccin geregistreerd te worden zodat ze zo nodig te herleiden zijn naar ieder individueel kind.

6 Bijwerkingen

Na vaccinaties kunnen bijwerkingen optreden. Meestal betreft dit lichte, veelal lokale verschijnselen. Elke bijwerking, zeker de ernstige, kan de vaccinatiegraad negatief beïnvloeden. Er wordt dan ook dringend verzocht elke ernstige, onverwachte of onrust veroorzakende (mogelijke) bijwerking te melden aan het Centrum Infectieziektebestrijding te Bilthoven, onder vermelding van het partijnummer van het betreffende vaccin (tel. 030 274 24 24;
fax. 030 274 44 30; Email: libris@rivm.nl).

7 Vaccinatieschema per kind

Leeftijd	Vaccinaties
0 maanden (<48 uur)	Hep B-0*
2 maanden	DKTP-Hib-1 + Hep B-1*
3 maanden	DKTP-Hib-2
4 maanden	DKTP-Hib-3 + Hep B-2*
11 maanden	DKTP-Hib-4 + Hep B-3*
14 maanden	BMR-1 + Men C
4 jaar	DTP-5 + aK
9 jaar	DTP-6 + BMR-2

* Alleen voor de in paragraaf 2 van deze richtlijnen omschreven doelgroepen

8 Entadministraties

Voor inlichtingen met betrekking tot het Rijksvaccinatieprogramma en over de wijze van uitvoering kan men zich wenden tot de voor de regio betreffende entadministratie.

Groningen / Friesland / Drenthe (Noord-Nederland)
Postbus 4050, 9701 EB Groningen
tel. 050-368 6350
fax. 050-312 2733
Email: info@stenn.nl

Overijssel / Flevoland*
Postbus 43, 7730 AA Ommen
tel. 0529-455 717
fax. 0529-455 805
Email: info@entorganisatie.nl

Gelderland*
Postbus 357, 6800 AJ Arnhem
tel. 026-442 9242
fax. 026-443 4999
Email: ent@spog.nl

** Verhuisd per 1-1-2006 als stichting Prepare naar Deventer.*

Utrecht / Noord-Holland
Postbus 1097, 3600 BB Maarssen
tel. 0346-550 040
fax. 0346-573 795
Email: algemeen@entutrecht.nl

Amsterdam
Postbus 2200, 1000 CE Amsterdam
tel. 020-555 5460
fax. 020-555 5071
Email: jgzent@ggdamsterdam.nl

Zuid-Holland
Postbus 654, 2700 AR Zoetermeer
tel. 079-341 8238
fax. 079-331 5047
Email: ent@rrezuidholland.nl

Rotterdam
Postbus 70032, 3000 LP Rotterdam
tel. 010-433 9518
fax. 010-433 9652
Email: ent@ggd.rotterdam.nl

Zeeland
Postbus 53, 4460 AB Goes
tel. 0113-224 080
fax. 0113-224 055
Email: entadministratie@spkez.nl

Noord-Brabant
Postbus 8220, 5004 GD Tilburg
tel. 013-540 0688
fax. 013-540 0086
Email: spen@peab.nl

Limburg
Postbus 5148, 6130 PC Sittard
tel. 046-452 9910
fax. 046-458 4479
Email: info@entadm-limburg.nl

Informatie over algemene, landelijke zaken de entadministraties betreffend kunt u verkrijgen bij:

LVE (Landelijke Vereniging van Entadministraties)
Postbus 100, 3980 GB Bunnik
tel. 030-299 3187
fax. 030-242 0874
Email: lve@entadministraties.nl

Meer achtergrondinformatie over het Rijksvaccinatieprogramma is te vinden op www.rvp.nl

Prof. dr. R. A. Coutinho
Directeur Centrum Infectieziektebestrijding

Bilthoven, december 2005

rijksVaccinatieprogramma

Appendix 2 Resume Product Information

Vaccines in RVP	Producer	constituents	
DTP-IPV-Hib vaccine Diphtheria, acellular Pertussis, Tetanus and inactivated Poliomyelitis vaccine mixed with conjugated Hib-vaccine 0.5 ml	Aventis Pasteur RVG 32118	Diphtheria toxoid Tetanus toxoid Pertussis toxoid (PT) Filamenteuze hemagglutinine (FHA) Fimbriae agglutinogenen 2 and 3 (FIM) Pertactin (PRN) Inactivated poliovirus type 1 (Mahoney) Inactivated poliovirus type 2 (MEF-1) Inactivated poliovirus type 3 (Saukett) Haemophilus influenzae type b polysaccharide Conjugated to tetanus toxoid (PRP-T)	≥30 IE ≥ 40 IE 20µg 20µg 5µg 3µg 40 DE 8 DE 32 DE 10µg 20µg
DTP-IPV-Hib-HepB vaccine Diphtheria, acellular Pertussis, Tetanus, inactivated Poliomyelitis and Hepatitis B vaccine mixed with conjugated Hib-vaccine 0.5 ml	GSK EU/1/00/152/001 EU/1/00/152/002 EU/1/00/152/003 EU/1/00/152/004 EU/1/00/152/005 EU/1/00/152/006 EU/1/00/152/007 EU/1/00/152/008	Diphtheria toxoid* Tetanus toxoid* Pertussis toxoid* (PT) Filamenteuze hemagglutinine* (FHA) Pertactin* (PRN) Hepatitis-B**,*** Inactivated poliovirus type 1 (Mahoney) Inactivated poliovirus type 2 (MEF-1) Inactivated poliovirus type 3 (Saukett) Haemophilus influenzae type b polysaccharide*** Conjugated to tetanus toxoid (PRP-T) *adsorbed to aluminiumhydroxide **produced in yeast (Saccharomyces cerevisiae) by recombinant DNA techniques ***adsorbed to aluminium phosphate	≥30 IE ≥ 40 IE 25µg 25µg 8µg 10µg 40 DE 8 DE 32 DE 10µg 20-40µg 0,95mg 1,45mg
DTP-IPV vaccine Diphtheria, Acellular Pertussis, Tetanus and inactivated Poliomyelitis vaccine 0,5 ml	Sanofi Pasteur RVG 27569	Diphtheria toxoid Tetanus toxoid Pertussis toxoid (PT) Filamentous hemagglutinin (FHA) Fimbriae 2 and 3 (FIM) Pertactin (PRN) Inactivated poliovirus type 1 Inactivated poliovirus type 2 Inactivated poliovirus type 3 adsorbed to aluminium phosphate	≥ 2 IE ≥ 20 IE 2,5 µg 5µg 5µg 3µg 40 DE 8 DE 32 DE 0,33 mg Al
DT-IPV vaccine Diphtheria, Tetanus and inactivated Poliomyelitis vaccine 1 ml	NVI RVG 17641	Diphtheria toxoid * Tetanus toxoid* Inactivated poliovirus type 1 Inactivated poliovirus type 2 Inactivated poliovirus type 3 *adsorbed to aluminium phosphate	≥ 5 IE ≥ 20 IE ≥ 20 DE ≥ 2 DE ≥ 3.5 DE 1,5 mg
Pertussis vaccine 3 component acellular pertussis vaccine 0.5 ml	GSK RVG 22335	Pertussis-toxoid (PT) Filamentous hemagglutinin (FHA) Pertactin	25µg 25µg 8µg
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	2µg 4µg 2µg 2µg 2µg 2µg 2µg 0,5 mg

MMR vaccine Mumps, measles and rubella vaccine 0.5 ml	NVI RVG 17654	Mumps virus ≥ 5000 p.f.u. Measles virus ≥ 1000 p.f.u. Rubella virus ≥ 1000 p.f.u.
Meningococcal C vaccine Conjugated menC vaccine 0.5 ml	Baxter RVG 26343	Neisseria meningitidis (C!!-strain) Polysaccharide ()-deacetylated 10µg Conjugated to Tetanus toxoid 10-20 mg Adsorbed to aluminium hydroxide 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) 5µg Adsorbed to amorphe aluminiumhydroxy-phosphatesulphate 0.25mg *yeast strain Saccharomyces cerevisiae (2150-2-3)

For full product information see www.cbg-meb.nl