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Adverse Events Following Immunisation under the National Vaccination Programme of the Netherlands
Number XII - Reports in 2005

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Het rapport in het kort

Postvaccinale gebeurtenissen binnen het Rijksvaccinatieprogramma
Deel XII- Meldingen in 2005

De bijwerkingenbewaking van het Rijksvaccinatieprogramma over 2005 liet een duidelijke afname zien van het aantal meldingen met 52%. Dit betrof vooral een daling van meldingen na DKTP-Hib vaccinaties. De daling in het aantal meldingen is toe te schrijven aan de overgang naar een acellulair DKTP-Hib vaccin. In 2005 zijn in totaal 1036 meldingen ontvangen. Hiervan werd 73% als bijwerking van de vaccinaties beschouwd. De rest (27%) 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 1036 meldingen betrof het in 752 (73%) gevallen een bijwerking. Hierbij ging het in 47% om heftiger verschijnselen, met name zeer hoge koorts, langdurig huilen, collapsreacties en verkleurde benen. Hierbij waren 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 2005; 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 acht 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 XII - Reports in 2005

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 2005 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 1036 AEFI were reported. Of these, 5 (0.5%) were unclassifiable because of insufficient information. In 73% (752) of the classifiable events a possible causal relation with vaccination was established. These concerned major adverse reactions in 47% and minor adverse reactions in 53% of the reports. Of the reported adverse events 27% (279) were considered chance occurrences. Compared to 2004 and 2003 there was a decrease in number of reports with 52% and 25%, respectively. The huge increase is 2004 was caused by repeated media attention about the safety of the formerly used whole cell pertussis vaccine. The decrease in 2005 was caused by the use of a new, acellular DPTP-Hib vaccine. The Netherlands Vaccination Programme has a very favourable risk balance.

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

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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 2005 is het twaalfde jaarrapport.
Van de meldingen kwam 89% telefonisch binnen. Meldingen kwamen merendeels vanuit de Jeugdgezondheidszorg (75%). 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 (92%) alleen telefonisch aan de melder teruggerapporteerd. Schriftelijk verslag van geselecteerde, ernstigere of gecompliceerde ziektebeelden, werd naar alle medisch betrokkenen gestuurd.
In 2005 zijn 1036 meldingen ontvangen, over 960 kinderen, op een totaal van meer dan 1,4 miljoen vaccinatiemomenten. Vijf meldingen (0,5%) waren niet te beoordelen wegens ontbrekende informatie. 752 Meldingen (73%) werden als bijwerking beoordeeld met mogelijk, waarschijnlijk of zeker causaal verband met de vaccinaties. Een toevallige samenloop werd aangenomen bij 279 (27%) meldingen.
Van de 544 gemelde mildere, zogenaamde “minor” algemene ziekte-, huid- of lokale verschijnselen werd 70% (378) als mogelijke bijwerking geduid. Gemelde zogenoemde “major” postvaccinale gebeurtenissen (492) werden in 77% (375) 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 (57) hadden op drie na een mogelijke causale relatie met de vaccinaties.
Collaps, waaronder atypische en onvolledige episodes, werd 75 maal vastgesteld, in 16 gevallen zonder oorzakelijk verband. Daarnaast waren er enkele breath-holding-spells (6), twee keer zonder oorzakelijk verband, en flauwvallen (52) in oudere kinderen.
Stuipen (71) gingen op zes na alle gepaard met koorts. Van de convulsies werden er 57 als mogelijke bijwerking beoordeeld. Van de 43 atypische aanvallen hadden er 29 een mogelijk causaal verband. Epilepsie (4) werd in geen van de meldingen als bijwerking geduid, maar als ongerelateerd aan de vaccinatie.
Persistent screaming (58) werd in 54 gevallen als bijwerking beschouwd.
Koorts van ≥40,5°C was de werkdiagnose bij 40 kinderen uit de “ziek-major”-groep, op 12 na alle beschouwd als mogelijke bijwerking. Van de 57 andere beelden uit de “ziek major” groep was er 21 keer een mogelijk causaal verband. Dit betrof vaccinitis (12) gepaard aan

zeer hoge koorts (≥40,5^{o}C), tekort aan bloedplaatjes (Idiopathische Trombocytopenische Purpura, n=5), artritis/osteomyelitis (3) en apneu(1).
Er waren 13 abcessen, waarvan vijf na BCG-vaccinatie. Van zeven abcessen is bekend dat er gekweekt is; vier waren positief streptokokken groep A, één voor pneumokok, twee toonden geen groei.
In 2005 is één kind met encefalopathie /-itis gemeld, niet causaal gerelateerd aan de prik, maar berustend op een andere oorzaak.
De acht sterfgevallen die in 2005 zijn gemeld, zijn alle na uitgebreide evaluatie als coïncidentele gebeurtenis beoordeeld. Drie kinderen hiervan zijn late, nagekomen meldingen over eerdere jaren. Bij vier kinderen is obductie verricht; hierdoor is bij één kind een myocarditis geconstateerd en bij drie kinderen de diagnose wiegendood gesteld. Bij vier andere kinderen is de diagnose klinische wiegendood gesteld, omdat er geen obductie is verricht en er geen andere aannemelijke verklaringen waren voor het overlijden.
De meeste meldingen (593) 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 315 van de meldingen, waarvan 275 maal gecombineerd met andere vaccins. In 61% was er een mogelijke causale relatie met de BMR. Dit was 60% voor de andere vaccin(combinatie)s.
Vergeleken met 2003 en 2004 was er een forse daling in het aantal meldingen. Deze is toe te schrijven aan het gebruik van een nieuw, acellulair DKTP-Hib vaccin.
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 have 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 2005 is the twelfth annual report.
The majority of reports (89%) came in by telephone. Child Health Clinic staff are the main reporters (75%). 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 (92%). Written assessments of selected more serious or complicated events, were sent to all medical professionals involved.
In 2005, on a total of over 1.4 million vaccination dates, 1036 AEFI were submitted, concerning 960 children. Of these only five (0.5%) were not classifiable because of missing information. Of the classifiable events 752 (73%) were judged to be possibly, probably or definitely causally related with the vaccination (adverse reactions) and 279 (27%) were considered coincidental events.
So-called "minor" local, skin or systemic events were assessed in 544 cases with 378 reports (70%) 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 492 cases. In 77% (375) these were considered possible adverse reactions.
Discoloured legs were reported 57 times with possible causal relation in all but three.
Collapse, including atypical and incomplete episodes, was diagnosed 75 times, in only 16 cases without causal relation. Six breath holding spells were reported, in four with inferred causality and 52 times fainting in older children.
Convulsions were diagnosed in 71 cases, in all but six with fever. Of the convulsions 57 were considered causally related. Atypical attack (43) had possible causal relation in 29 of cases. Epilepsy (4) was considered not causally related with the vaccinations in all instances.
Of persistent screaming 54 out of 58 reports were considered adverse reactions.
Fever of $\geq$40.5°C was the working diagnosis in 40 reports of the major-illness group, in all but 12 with inferred causality. Of the other 57 major-illness cases 21 had a possible causal relation. These events were "vaccinitis" (12) all with very high fever ($\geq$40.5^{o}C), ITP (5), arthritis/osteomyelitis (3) and apnoea (1).
There were 13 abscesses, five times occurring after BCG. Four cultures were positive for Haemolytic Streptococcus group A and one for Streptococcus Pneumoniae. Two cultures showed no growth.

One case of encephalopathy /-itis was reported in 2005, not induced by the vaccination but considered coincidental.
In 2005 all eight reported deaths were considered chance occurrences after thorough assessment. Three of these children considered late reports, death occurring in previous years. Four children were examined post mortem. One child had myocarditis, the other three were SIDS. The other four children were diagnosed as clinical SIDS because no autopsy was performed and there was no plausible explanation for diagnosed as death.
Most frequently (593) 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 315 times, 275 times with simultaneous other vaccines. In 61% of these reports there was possible causal relation with MMR. For the other vaccine combinations this percentage was 60%.
In 2005 the number of reports decreased with 52% and 25% compared to 2004 and 2003, respectively. This was due to the use of a new, acellular DPTP-Hib vaccine.
The total of 1036 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 2005. 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 change to an acellular DPTP-Hib vaccine for infants in January 2005. In 2004 there was repeated adverse publicity on the safety of the whole cell pertussis vaccine. This resulted in a steep rise in the number of reported AEFI in 2004. 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.
Below we will go into the number of reports and the different aspects of the nature of the reported adverse events in 2005.
This twelfth 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 2005

2 months	DPTP1	+	Hib1	+	HepB1*
3 months	DPTP2	+	Hib2		
4 months	DPTP3	+	Hib3	+	HepB2
11 months	DPTP4	+	Hib4	+	HepB3
14 months	MMR1	+	MenC*		
4 years	DTP5	+	aP		
9 years	DTP6	+	MMR2		

* = MenC for children born from 1 June 2001 and HepB for risk group children born from 1 January 2003

In the year under report the whole cell pertussis containing DPTP-Hib vaccine was replaced by an acellular DPTP-Hib combination vaccine. [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]
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.
DTPolio and MMR are produced by NVI (Netherlands Vaccine Institute); DPTP-Hib is from GlaxoSmithKline(GSK). This company produces also aP. MenC-vaccine is from Baxter. HepB is produced by SPMSD. SerumStatenInstitute produces BCG. (Summarised product characteristics in Appendix 2 and full documents 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 DTP and aP is usually given at the last CB visit, before school entrance. Booster vaccination with DTP 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 DPTP/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 the surveillance of effectiveness are performed by the Department for Infectious Diseases Epidemiology (CIE), independently from vaccine manufacturers. [11] CIE 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. The national guideline book on the RVP with background, execution and procedures contains a (RIVM written) chapter on possible side effects and gives ample information on notification procedures. [3]

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] 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. [51]

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). [3,39,52,53]

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. 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 ≥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 5).

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 6).
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 occurence. 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. A physician of RIVM is advisory member of this GR committee. Summarised reassessments of the GR committee have been published in annual GR reports to the Minister of Health, Welfare and Sport. [54,55,56]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 annually, or more often when necessary, linelistings of all adverse events (AE) to the specific vaccine manufacturers that contribute to the National Vaccination Programme.

4 Results

4.1 Number of Reports

In 2005 RIVM received 1036 notifications of adverse events, on a total of 1.4 million vaccination dates with nearly 7 million vaccine components administered (Table 1). These 1036 reports involve 960 children. 47 Notifications were multiple with two (or more) events after different vaccination dates in an individual child resulting in 99 reports. 23 Notifications were compound with two (or more) distinct adverse events after one vaccination (date). One of these compound reports was also multiple. See paragraph 3.2 for definitions.
Multiple and compound reports are listed under the respective event categories. As described in paragraph 3.2, notifications concerning more than one vaccination date with only mild or common symptoms were booked as single reports unless reported on different dates.

Table 1. Number and type of reports of notified AEFI in 2000-2005

notifications 2005	children	adverse event reports	reports 2004	2003	2002	2001	2000
single	890[a]	890	1756	1166	1174	1178	1036
multiple	47[b]	99	280	151	111	133	79
compound	22[c]	44	80	41	34	16	24
compound and multiple	1	3	25	16	13	4	3
total	960	1036	2141	1374	1332	1331	1142

[a] 42 children had also reports in previous (33) or following (9) years; these are not included
[b] two children with triple reports and one child with a quadruple report
[c] all children had double reports

From 1994 onwards comparisons of numbers are valid because the criteria for recording have been consistent. Even without exact counts of previous years, it is clear that the number of reported events increased in 1994 and 1995 with levelling off in 1996 and 1997 (Table 2). This was considered to be due to decreased underreporting. [41,40,41] In 1998 there was a significant increase in the number of reports judged to be partly due to increased awareness and apprehension, to further reduced underreporting but also to some genuine increase in actual adverse reactions. [42] In 1999 there was again an increase in the number of reports. This was to be expected because the shift in the schedule, with start at two months of age from March 1999 onwards, resulted in a larger number of vaccinated infants; for dose 1, 2 and 3 approximately an extra 50,000 DPTP-Hib vaccinations. [43] In 2001 there was another increase in the number of reports judged to be possibly due to intensified follow up of the reports both by reporters and by RIVM. Also some better adherence to the accelerated schedule may have played a role, resulting in vaccination on average at a younger age. This might have yielded a

higher number of reports of some more young-age specific events. [45,46] In 2003 implementation of MenC vaccination and HepB vaccine for risk groups may have contributed to some increase in reports respectively (www.rivm.nl). [2,49,57] The increase in 2004 followed adverse publicity on the safety of the DPTP-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. [1] In 2005 for the first time in years the number of reports has gone down, both for single events as for compound and multiple events. Details will be given in the paragraphs below and inference in the discussion.
The birth cohort has increased gradually up till 2000 from nearly 190,000 in 1996 to over 206,000 in 2000. Since then there is gradual decrease to a little below 188,000 in 2005. [58]

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

year of notification	written assessments	total[b]
1984	91	310
1985	139	325
1986	197	350
1987	149	325
1988	143	390
1989	141	440
1990	128	375
1991	136	340
1992	147	440
1993	227	496
1994	276	**712**
1995	234	800
1996	141	732
1997	76	822
1998	48	**1100**
1999	74	1197
2000	65	1142
2001	116	**1331**
2002	81	1332
2003	172	1374
2004	143	**2141**
2005	84	**1036**

[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

The reporter is the first person to notify RIVM about the adverse event (Figure 1). As in previous years the vast majority of reports came by telephone (Table 3). We received 116 (11.2%) written reports of which 68 reports by regular mail, 31 by e-mail and 17 by fax (range 3.3%-12.9% for 2000-2004). Some (18) of these written reports are from inclusion of some of the RIVM questionnaire reports from active studies. Criteria for inclusion of these questionnaires in this annual report were severity, rarity or extreme (public) concern. See paragraph 3.2. Questionnaire information obviously has also been included if the event was reported independently by another reporter.

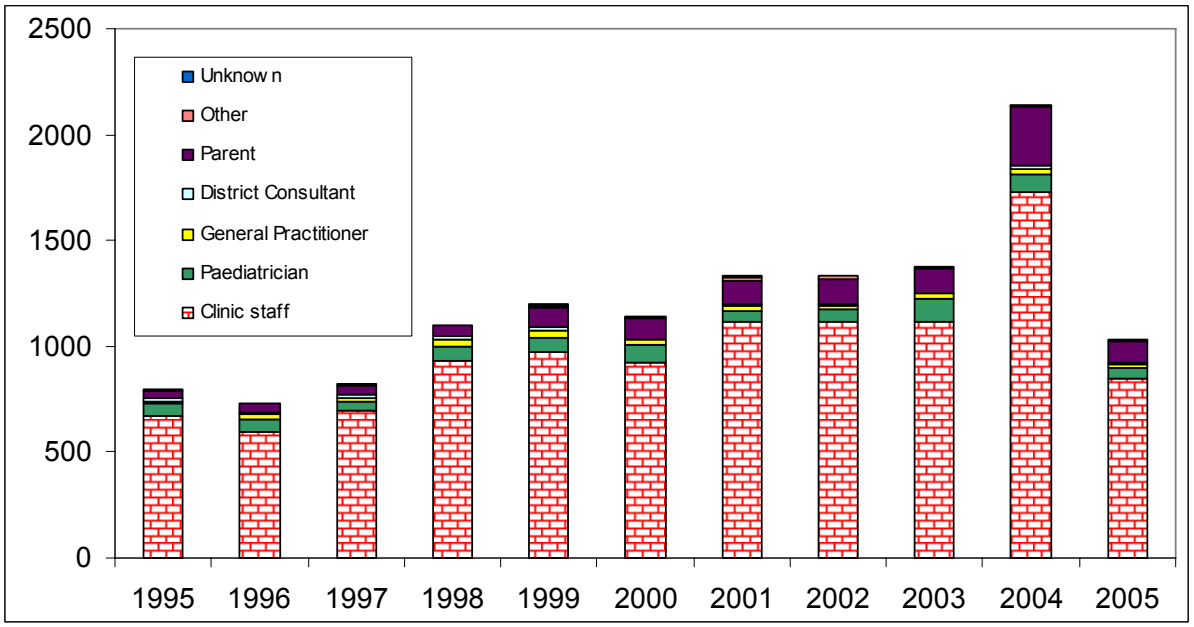


Figure 1. Reporters of adverse events following vaccinations under the RVP

Child Health Clinics accounted for 775 reports (75%). In 2000-2004 this varied between 78% and 81%. Parents of 102 children (9.8%) were the primary reporters (range 8.2%-12.6% in 2000-2004). The share of the Municipal Health Service has increased to 7.3%. In 2000-2004 this fluctuated from 2.0% to 3.2%. The share of other report sources was more or less stable (detailed information in Table 3).

Table 3. Source and reporting route of AEFI in 1995-2005

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	*tel*	*mail*[c]
Clinic staff[a] Physician	548	466	547	678	722	687	794	791	741	1199	547	*512*	*35*
Nurse	102	116	142	219	221	199	290	282	337	486	228	*223*	*5*
Paediatrician	59	56	39	69	70	80	56	61	108	84	48	*34*	*14*
General Practitioner	13	26	20	35	34	28	18	17	22	24	13	*13*	*0*
Municipal Health Service	18	17	10	31	27	37	31	39	39	44	76	*47*	*29*
District Consultant	18	11	16	15	16	5	11	8	5	21	12	*12*	*0*
Parent	34	35	40	52	91	97	115	121	113	271	102	*72*	*30*
Other[b]	6	2	7	1	9	7	14	13	9	12	10	*7*	*3*
Unknown	2	3	1	-	7	2	2	-	-	-	-	-	-
total	800	732	822	1100	1197	1142	1331	1332	1374	2141	1036	*920*	*116*
(% written)	(3.4)	(3.4)	(6.2)	(2.3)	(3.8)	(3.3)	(3.8)	(4.9)	(7.9)	(12.9)	(11.3)		

[a] including staff of refugee clinics (5)
[b] including reports by Lareb (2), manufacturer (1), LWW (4) and general public (3)
[c] including e-mail (31) and fax (18) reports

In 2005 the reporter was the sole informer in 12%. Information was received from others also in 88%, both spontaneously and requested (range 67-87% for 2000-2004). The clinics (child health, school health and refugee clinics) supplied information in 94.5%, a little more than 2004 and 2003 (93%). Parents were contacted in 89% (917), sometimes during the notifying telephone call from the Child Health Clinic (range 66%-90% for 2000-2004). Reports in which the parents were the sole informers (31) are included. Hospital specialists supplied information in 18% of the reports (range 16%-24% for 2000-2004). See for details Table 4.

Table 4. Information sources and type of events in reported AEFI in 2005

															total (%)
info ⇒	clinic*	+	+	+	+	+	+	+	-	-	-	-	-	-	979 (94.5)
	parent	-	+	+	+	+	-	-	+	+	+	-	-	-	917 (88.5)
	gen. pract.	-	-	-	+	+	-	+	+	-	-	+	-	-	40 (3.9)
	hospital	-	-	+	-	+	+	-	-	+	-	-	+	-	190 (18.3)
event ⇓	other	-	-	-	-	-	-	-	-	-	-	-	-	+	5 (0.5)
local reaction		12	55	11	5	-	1	1	-	-	8	-	-	-	93
general illness	minor	27	298	31	8	1	2	2	2	3	13	-	-	2	389
	major	6	42	25	2	5	7	-	-	5	2	1	2	-	97
persistent screaming		2	54	1	-	-	-	-	-	-	1	-	-	-	58
skin symptoms		4	64	4	4	-	-	-	-	2	3	-	-	1	82
discoloured legs		5	43	9	-	-	-	-	-	-	-	-	-	-	57
faints		28	80	19	-	-	1	1	-	1	3	-	-	-	133
fits		3	56	42	5	2	4	-	-	3	1	-	2	-	118
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-	0
encephalopathy/-itis		-	-	1	-	-	-	-	-	-	-	-	-	-	1
death				2		1	3							2	8
total		87	692	145	24	9	18	4	2	14	31	1	4	5	1036

* 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. This feedback, both to professionals and parents, is mostly done by telephone. A full written assessment followed 84 (8.1%) reports (range 6%-12% for 2000-2004, Table 5). These concerned the more complex events or those causing (public) anxiety or extreme uncertainty about subsequent vaccinations. Our intention is to supply a comprehensive written feedback with assessment and advice routinely.

Table 5. Feedback method and events of reported AEFI in 2000-2005

		2000		2001		2002		2003		2004		2005	
event ⇓ feedback method⇒		mail	total	mail	total	mail	total	mail	total	mail	total	mail	total
local reaction		3	75	1	90	1	120	4	123	4	129	2	93
general illness	minor	8	366	21	447	12	417	16	460	16	704	13	389
	major	18	106	14	74	20	112	51	119	33	198	30	97
persistent screaming		-	39	2	49	1	46	2	55	3	133	1	58
skin symptoms		-	75	0	73	-	104	5	104	3	106	2	82
discoloured legs		5	126	14	175	4	137	9	134	15	279	2	57
faints		17	239	34	293	20	297	35	244	25	378	6	133
fits		15	112	22	121	16	91	47	132	37	211	20	118
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		1	1	2	2	-	-	-	_	3	3	-	1
death		3	3	7	7	8	8	3	3	4	4	8	8
total		70	1142	116	1331	82	1332	172	1374	143	2141	84	1036

4.3 Regional Distribution

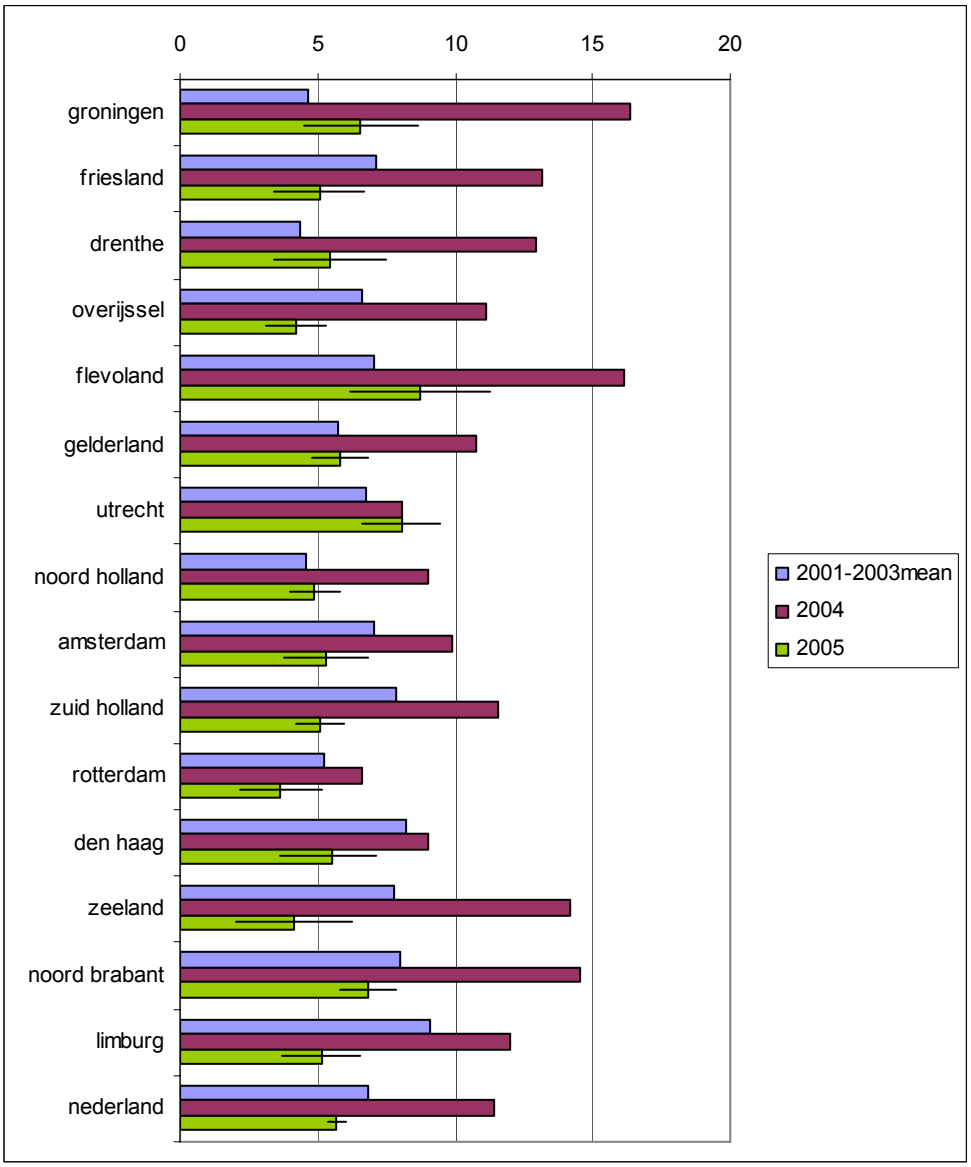
Reports come from all over the country but are not evenly spread. Standardisation of the rate per 1000 vaccinated infants is done according to coverage data from the PEA. In 2005 the PEA adopted a new centralised web based vaccination register, Praeventis. In Table 6 the rates were calculated with vaccination coverage data of Praeventis for the corresponding year. As before, we used the coverage data for the first three DPTP doses; only for 2005 the coverage data for the first DPTP dose were used. Since the regular summarised reports of coverage data do not contain information on timing of the vaccination there will remain inevitably some inaccuracies in estimated rates per region.
The birth cohort increased from a little below 190,000 in 1996 to 206,619 in 2000. Subsequently the birth cohort decreased yearly to 187.884 in 2005. [58] The reporting rate was 5.7 per 1000 vaccinated infants (DPTP-Hib1) in 2005. Range for 2000-2004 is 5.6-11.4 (DPTP3). There was less dispersion of the reporting rates over the different regions, compared to 2004, but similar to 2001-2003.

Table 6. Regional distribution of reported AEFI in 2000-2005, per 1000 vaccinated infants[a] with proportionate confidence interval for 2005 (major adverse events)

	2000 (major)	2001 (major)	2002 (major)	2003 (major)	2004 (major)	2005 (major)	95% c.i. 2005 (major)
Groningen	5.5 (3.7)	4.5 (3.4)	4.1 (2.5)	5,4 (2.8)	16.4 (9.6)	6.6 (2.4)	4.5-8.6 (1.2-3.7)
Friesland	5.5 (3.6)	6.4 (3.2)	7.6 (4.8)	7,5 (4.4)	13.1 (7.8)	5.1 (3.0)	3.4-6.7 (1.8-4.3)
Drenthe	4.7 (2.5)	3.7 (2.0)	3.1 (2.2)	6,4 (3.7)	12.9 (10.3)	5.4 (2.7)	3.4-7.5 (1.3-4.2)
Overijssel	6.3 (3.1)	6.0 (3.3)	6.4 (3.7)	7,4 (3.3)	11.2 (5.8)	4.2 (1.6)	3.1-5.3 (0.9-2.3)
Flevoland	4.7 (3.0)	6.9 (4.1)	6.8 (3.4)	7,4 (4.2)	16.2 (9.0)	8.7 (3.7)	6.2-11.3 (2.0-5.4)
Gelderland	4.8 (2.8)	5.0 (2.9)	5.9 (3.2)	6.3 (3.0)	10.8 (5.8)	5.8 (2.4)	4.8-6.9 (1.8-3.1)
Utrecht	4.9 (2.4)	6.7 (3.4)	6.7 (3.1)	6,9 (3.2)	8.1 (4.8)	8.0 (4.6)	6.6-9.5 (3.5-5.7)
Noord-Holland[b]	5.5 (3.5)	5.0 (2.7)	4.2 (2.3)	4.6 (2.3)	9.0 (5.0)	4.9 (2.4)	4.0-5.8 (1.8-3.1)
Amsterdam	5.1 (2.4)	7.8 (3.5)	6.0 (2.6)	7.3 (4.0)	9.9 (4.2)	5.3 (2.1)	3.8-6.9 (1.1-3.0)
Zuid-Holland[b]	5.6 (3.1)	7.5 (4.0)	7.6 (3.8)	8.4 (4.5)	11.6 (6.2)	5.1 (2.5)	4.2-5.9 (1.9-3.1)
Rotterdam	5.3 (3.1)	5.4 (3.8)	5.6 (2.4)	4,7 (1.7)	6.6 (4.7)	3.6 (1.9)	2.2-5.1 (0.8-3.0)
Den Haag	6.8 (4.2)	8.9 (4.9)	6.1 (2.5)	9,7 (5.5)	9.0 (5.5)	5.5 (1.8)	3.7-7.1 (0.8-2.9)
Zeeland	5.6 (3.7)	7.7 (5.8)	7.1 (5.6)	8.5 (4.0)	14.1 (10.7)	4.1 (1.7)	2.1-6.2 (0.3-3.0)
Noord-Brabant	6.4 (3.2)	7.7 (4.3)	8.5 (4.8)	7,8 (4.2)	14.6 (8.5)	6.8 (3.3)	5.8-7.8 (2.6-4.0)
Limburg	6.2 (3.9)	8.5 (5.4)	10.3 (5.3)	8.5 (4.6)	12.0 (6.8)	5.1 (2.9)	3.7-6.6 (2.0-4.4)
Netherlands	5.6 (3.1)	6.6 (3.7)	6.7 (3.6)	7.1 (3.7)	11.4 (6.6)	5.7 (2.7)	5.4-6.0 (2.5-2.9)

[a] For 2002, 2003, 2004 and 2005 coverage data of the corresponding year out of Praeventis have been used.
[b] provinces without the three big cities (Amsterdam, Rotterdam, Den Haag)

The 95% confidence intervals for the reporting rates in the different regions contained the country's overall reporting rate in ten of the fifteen regions. The country's average reporting rate for major events is 2.7/1000. Range for 2000-2003 is 3.1-3.7, for 2004 the rate is 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 4.8. For more information see Table 6 and Figure 2.



* provinces without big cities Amsterdam, Rotterdam, Den Haag

Figure 2. Number of reported AEFI in 2001-2003, 2004 and 2005 per 1000 vaccinated infants (with 95% c.i. bars for 2005, proportional, normal approximation)

4.4 Vaccines

In 2005 most notifications were about recent vaccinations (all except 65). Some of these 65 late reports arose from concerns about planned booster vaccination or vaccination of younger siblings. In 22% of these cases the parents reported. The vaccine involved in these

late reports was most often DPTP-Hib (38) and MMR (23, of which 7 simultaneously with MenC). All reports are included in the tables.
In Table 7 scheduled vaccines and actually administered vaccines are listed. For the first time, reports on the first DPTP-Hib dose were not the most prevalent. The relative frequencies of involved vaccinations changed a little compared to previous years (Figure 4).

Table 7. Schedule and vaccines of reported AEFI in 2005

vaccine given⇒ / scheduled ⇓	dptp	dptp hib	dptp hib hepb	hib	mmr	mmr menc	dtp	ak	dtp ak	dtp mmr	menc	bcg	other[f]	total 2005	2004	2003	2002	2001	2000
at birth	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-
dptp1+hib1	1[a]	184[a]	19	1[b]	-	-	-	-	-	-	-	-	-	205	725	462	503	515	418
dptp2+hib2	2	148	3	-	-	-	-	-	-	-	-	-	-	153	379	229	212	229	191
dptp3+hib3	-	97	12	2	-	-	-	-	-	-	-	-	-	111	289	147	150	163	133
dptp4+hib4	1[b]	106[b]	10	1	-	-	1	-	-	-	-	-	-	119	340	193	161	172	166
dose?	-	3	-	-	-	-	-	-	-	-	-	-	-	3	3	3	5	3	6
mmr0	-	-	-	-	10	-	-	-	-	-	-	-	-	10	1	8	-	4	4
mmr1*	-	-	-	-	33[d]	210	-	-	-	-	3	-	-	246	225	173	150	139	141
dtp5+ak	3	1[e]	-	-	-	-	7	20	82	-	1	-	-	114	90	78	67	41	33
dtp6+mmr2	-	-	-	1	1	-	1[b]	-	-	58[c]	-	-	1	62	62	37	35	47	49
menc	-	-	-	-	-	-	-	-	-	-	5	-	-	5	19	34	38	-	-
other	-	-	-	-	-	-	-	-	-	-	-	7	1	8	6	10	11	18	1
total	7	539	44	5	44	210	9	20	82	58	9	7	2	1036	2141	1374	1332	1331	1142

[a] once with MMR0
[b] once with MenC
[c] once with Hib
[d] three times with DPTP-Hib and once with Hib
[e] once with MMR1
[f] once Influenza and once HepA

The total number of reported adverse events after DPTP-Hib doses was 593, considerably lower than in previous years (range in 2000-2003 is 882-1033; 1730 in 2004). 134 Of these reports concerned the whole cell vaccine and 459 the acellular DPTP-Hib. The reports concerning DPTP-Hib showed a normal seasonal variety, similar to previous years. There is no trend in levelling off during the year, despite the fact that the share of whole cell DPTP-Hib reports diminished. See Figure 3.

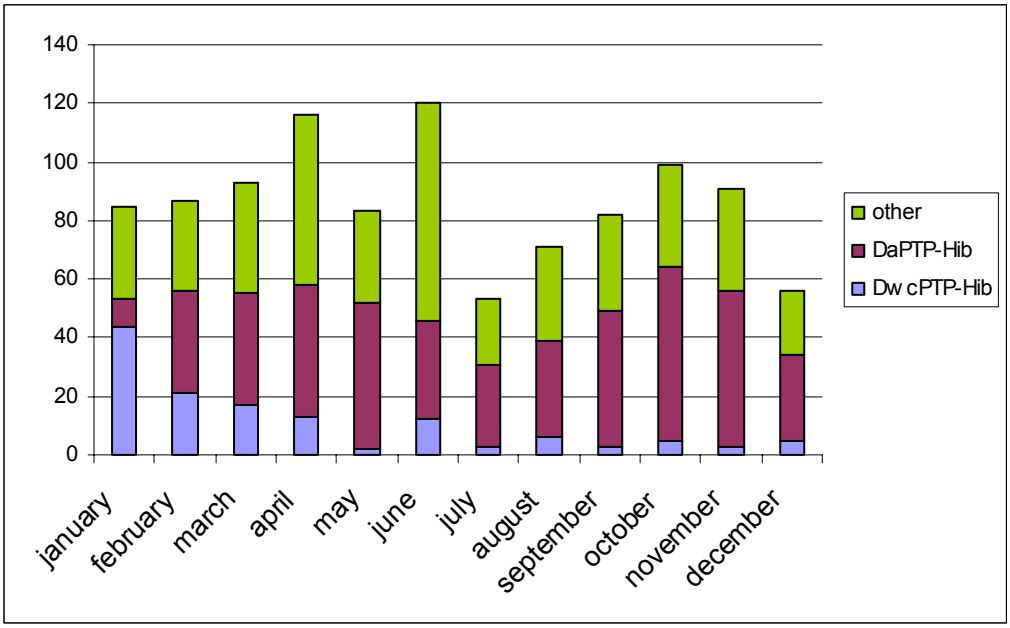


Figure 3: Absolute numbers of reports per month in 2005

44 Children received HepB vaccine simultaneously with DPTP-Hib as part of the programme for children with a parent from moderate and high-risk countries for hepatitis B carriage. Since the addition of MenC to the programme in 2002, simultaneously with MMR1, there has been an ongoing increase in reports at fourteen months; the same applies for reports after DTP5 at the age of four years since the introduction of simultaneous aK in 2002 for cohort 1998 onwards. Because of vaccine shortage approximately half a birth cohort received separate aK in 2005, resulting in 20 reports about single aK, compared to only seven reports about single DTP.
The number of reports (62) of events following DTP6/MMR2 is equal to 2004. Late reports of MenC in the campaign (5) are included in this report. The reported adverse events of the MenC campaign have been published separately. [59] Seven children were reported with events following BCG and two with non-RVP vaccines only. Further details in Table 7 and Figure 4. Specific vaccines and number of reports are listed in Table 9.

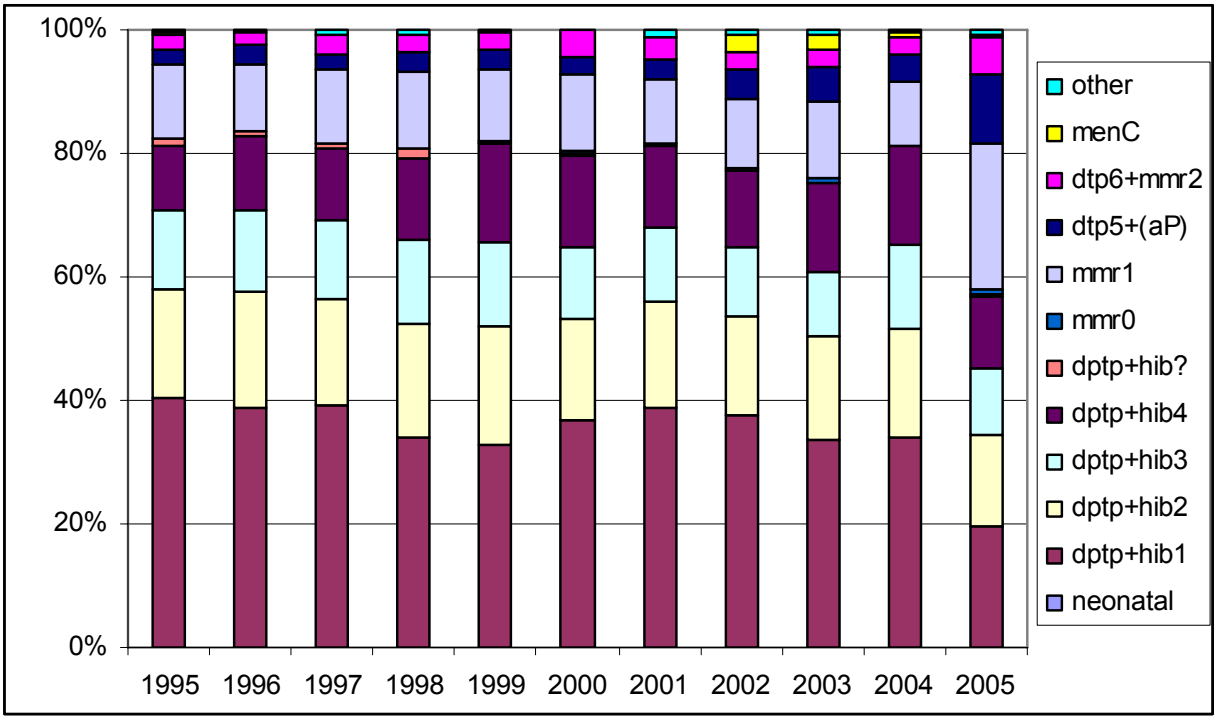


Figure 4. Relative frequencies of vaccine doses in reported AEFI in 1995-2005

Event categories are not equally distributed over the (scheduled) vaccinations (Table 8). Collapse and discoloured legs are most often reported after the first two vaccinations, as is persistent screaming.
Convulsions, especially febrile, are reported more frequently after the fourth DPTP-Hib and the first MMR/MenC. No children with anaphylactic shock were reported. One child with encephalopathy and eight children who died were reported. All events are listed here, irrespective of assumed causal relation. Consult for details the paragraphs on causality and on the specific events (4.7 and 4.8).

Table 8. Event category and (scheduled) vaccine dose of reported AEFI in 2005 (irrespective of causality)

event ⇓ vaccine⇒*	at birth	dptp hib1	dptp hib2	dptp hib3	dptp hib4	dptp hib?	mmr0	mmr1 menc	dtp5 ak	dtp6 mmr2	menc	other	Total 2005	2004	2003	2002	2001	2000
local reaction	-	7	5	5	16	-	-	9	40	5	-	6	93	129	123	120	90	75
general illness minor	-	88	52	42	49	2	3	101	28	22	1	1	389	704	460	417	447	366
major	-	8	14	13	10	-	5	40	1	4	2	-	97	194	119	112	74	106
persistent screaming	-	34	14	8	2	-	-	-	-	-	-	-	58	133	55	46	49	39
skin symptoms	-	14	13	10	10	1	1	23	5	3	1	1	82	106	104	104	73	75
discoloured legs	-	11	19	12	1	-	-	1	11	2	-	-	57	279	134	137	175	126
faints	-	29	29	12	7	-	-	5	25	26	-	-	133	378	244	297	293	239
fits	-	10	7	7	24	-	1	64	4	-	1	-	118	211	132	91	121	112
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	1	-	-	-	-	-	-	-	-	1	3	-	-	2	1
death	-	4	-	1	-	-	-	3	-	-	-	-	8	4	3	8	7	3
total	0	205	153	111	119	3	10	246	114	62	5	8	1036	2141	1374	1332	1331	1142

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

Compared to previous years the total number of reported events has decreased. Within and between the different event categories there are some changes. These will be commented upon also in the specific event paragraphs. However 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, compared to the years before introduction of acellular DPTP-Hib vaccine (Figure 5). General illness (minor and major) is still the largest category over the years, with a relative frequency of around 40%. The share of faints and discoloured legs decreased somewhat.

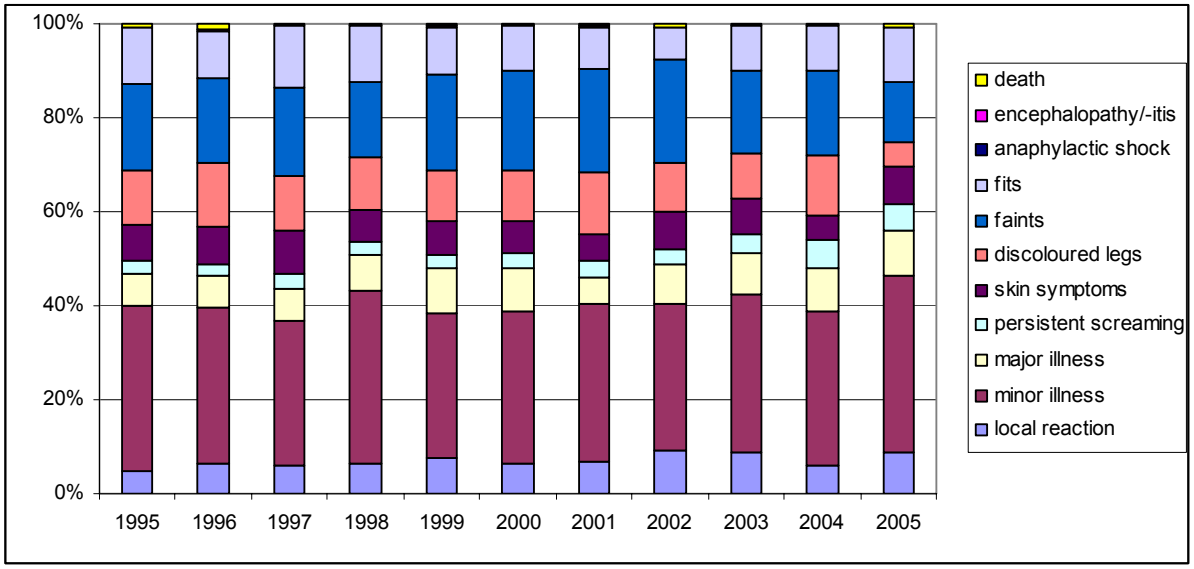


Figure 5. Relative frequencies of events in reported AEFI 1995-2005

The age distribution is given in Figure 6. The current database of the PEA does not allow a precise distribution curve of age at vaccination for the different vaccines for the denominator; only month of vaccination is registered for years before 2006.

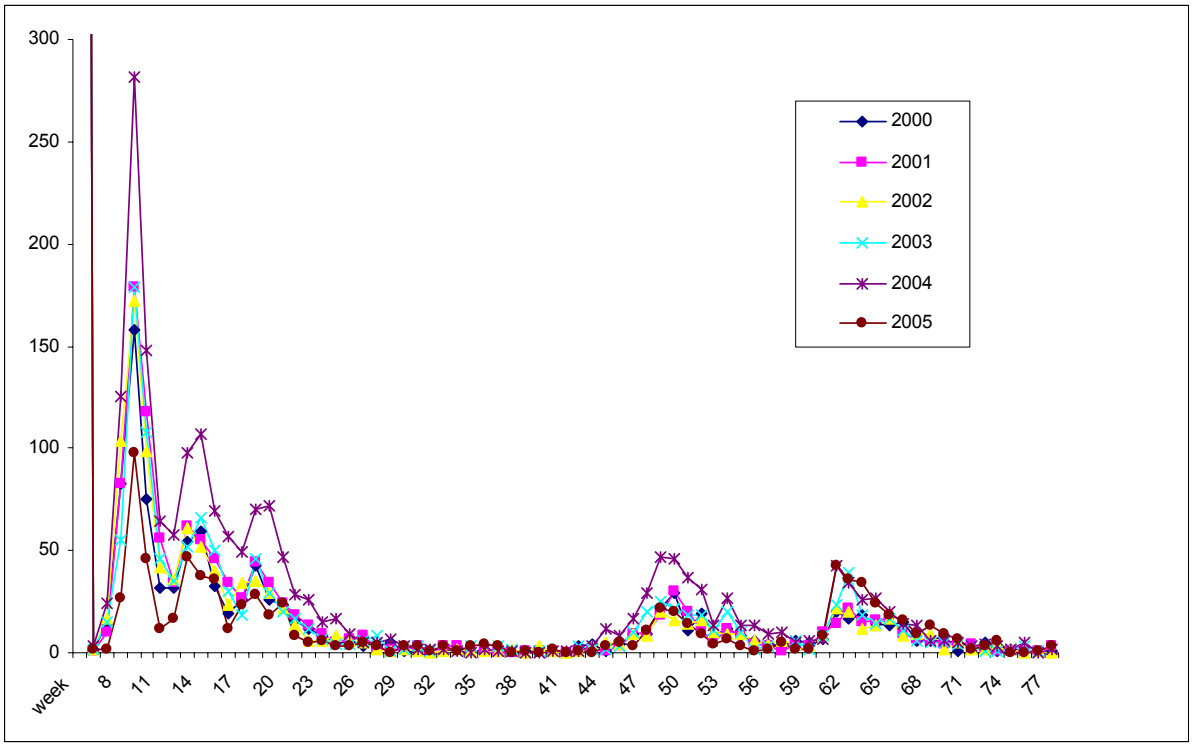


Figure 6. Age distribution of reported AEFI in 2000-2005

Table 9. Specific vaccines and number of reported AEFI in 2002-2005

vaccine, single or in combination	reports in 2005	2004	2003	2002	2001	2000
dptp	593[a]	1745	1037	1021	1073	904
hib[b]	593	1734	1029	1031	1053	897
mmr	315	283	222	188	193	192
menC	222	220	173	55	5	-
dtp	149	141	108	99	84	81
aK	102	67	67	56	7	-
hepB	44	153	55	3	3	1
other	9	8	10	11	13	2

[a] = 134 whole cell DPTP-Hib and 459 acellular DPTP-Hib.
[b] = mostly mixed with DPTP

4.5 Severity of Reported Events and Medical Intervention

The severity of reported adverse events is historically categorised in minor and major events. See for method description paragraph 3.5. The number of the so-called major events was 492 of 1036 (47.5%) with positive causality in 375 (36.4%). In 2000-2004 this ranged from

51.7%-57.7% with positive causality in 43.3%-50.5% (Figure 7). See also for causality paragraph 5.7.

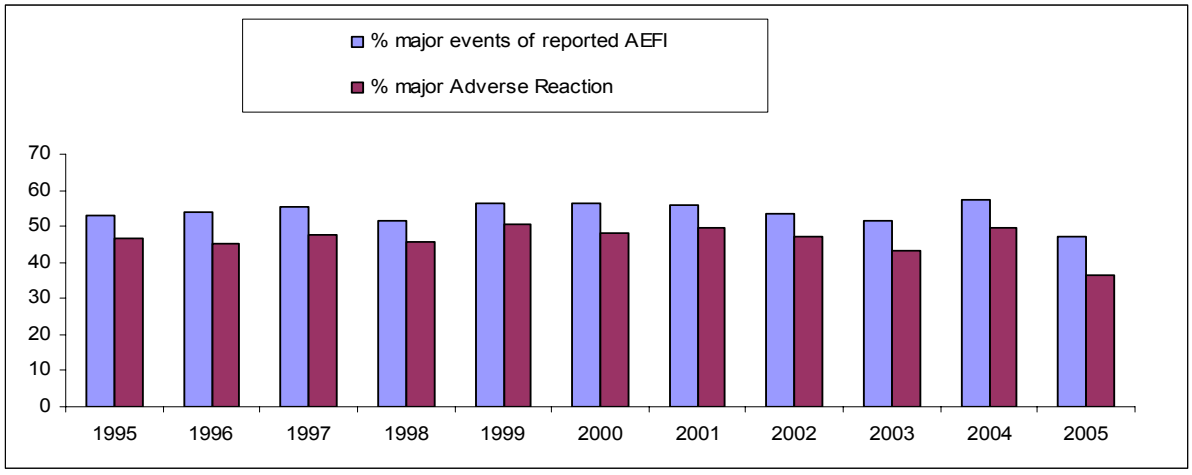


Figure 7. Proportion of reported major AEFI and major Adverse Reactions in 1995-2005

The level of medical intervention may also illustrate the impact of adverse events. In 17.6% (182) of reports either no medical help was sought or was not reported or recorded by us (range 16.2-22.4% for 2000-2004). Of the parents 13% (138) administered paracetamol suppositories, diazepam by rectiole or other home medication (range 12-27% for 2000-2004). In Table 10 and Figure 8 intervention is shown graded to level. In 69% parents contacted the clinic or GP, called the ambulance or went to hospital, with 11% admittance. For the five previous years these percentages varied from 57-67% and from 8-13% for hospital admittance.

Table 10. Intervention and events of reported AEFI in 2005 (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	4	20	9	18	5	26	-	4	1	6	-	-	93
general illness minor	21	65	70	34	26	118	-	20	10	16	9	-	389
major	5	2	4	-	10	25	2	7	7	33	2	-	97
persistent screaming	1	14	22	3	4	11	-	-	2	-	1	-	58
skin symptoms	6	6	6	6	6	38	-	7	3	-	4	-	82
discoloured legs	1	10	7	5	4	19	-	4	3	3	1	-	57
faints	2	17	12	49	5	22	4	4	7	11	-	-	133
fits	1	6	8	3	7	21	15	6	7	41	3	-	118
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	-	-	-	-	-	-	1	-	-	1
death	-	1	-	-	-	-	-	-	-	3	-	4	8
total 2005	41	141	138	118	67	280	21	52	40	114	20	4	1036

[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

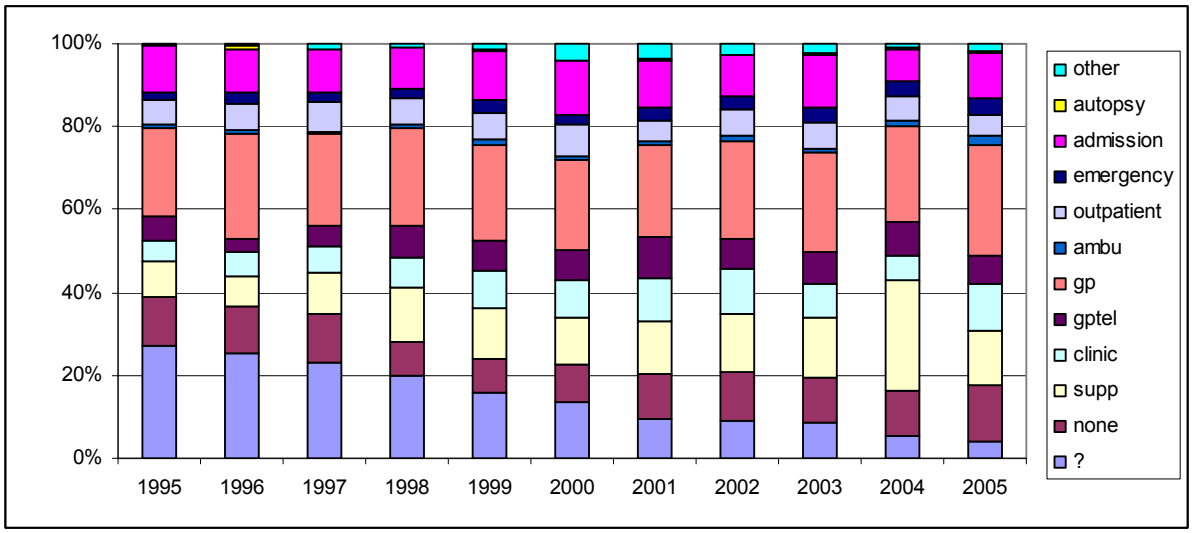


Figure 8. Level of medical intervention according to highest level used for AEFI 1995-2005

4.6 Sex Distribution

Over the years more boys than girls have been reported. Gradually this has "normalised". In 1994 and before 60% of the reports concerned boys, with a gradual decrease from 1995 to 1998 to 54%. Since then this percentage of reported boys ranged between 51-54%. In 2005 52% of the reported cases were male (Table 11 and Figure 9).

Table 11. Events and sex of reported AEFI in 2000-2005 (totals and percentage males)

event ⇓		sex⇒	m%	2000 total	m%	2001 total	m%	2002 total	m%	2003 total	m%	2004 total	m%	2005 total
local reaction			47	75	47	90	43	120	49	123	48	129	46	93
general illness		minor	57	366	55	447	53	417	57	460	56	704	55	389
		major	60	106	59	74	52	112	57	119	53	194	52	97
persistent screaming			54	39	57	49	61	46	56	55	50	133	47	58
skin symptoms			51	75	53	73	51	104	51	104	53	106	49	82
discoloured legs			52	126	42	175	51	137	42	134	53	279	51	57
faints	collapse		56	221	48	268	53	270	52	210	56	318	61	75
	BHS		60	5	40	5	50	8	44	9	52	23	17	6
	fainting		33	13	42	20	50	19	32	25	38	37	40	52
fits	convulsions		44	63	49	56	62	45	48	70	51	98	51	71
	epilepsy		14	7	20	10	80	5	40	5	33	9	50	4
	atypical attacks		60	42	63	55	50	41	60	57	63	104	58	43
anaphylactic shock			-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis			100	1	50	2	-	-	-	-	0	3	100	1
death			67	3	43	7	75	8	100	3	25	4	38	8
total			54	1142	51	1331	52	1332	52	1374	54	2141	52	1036

Distribution over the different events ranged from 40% boys for fainting to 61% boys with collapse (events with less than 40 reports excluded). Of four children the sex is not known.

See for specifics on the events and subdivision, the respective categories under paragraph 4.8.

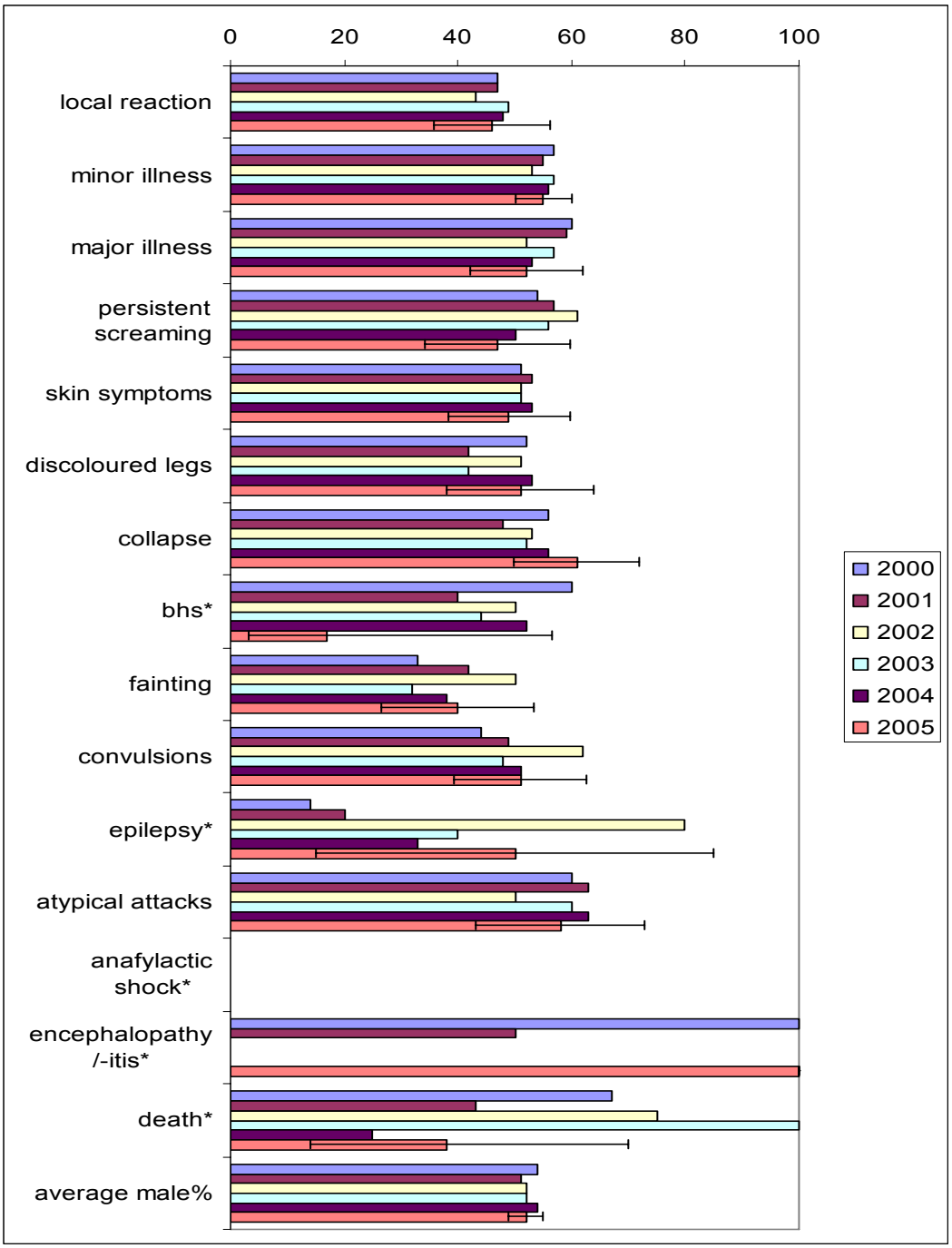


Figure 9. Events and sex ratio in reported AEFI in 2000-2005 with confidence intervals
*proportional with exact distribution

4.7 Causal Relation

Events with (likelihood of) causality assessed as certain, probable or possible are considered adverse reactions (AR). In 2005, 73% of reports were adverse reactions, with exclusion of the five non-classifiable events. Range for 2000-2004 is 78%-83%. The other events (280) were

considered coincidental with improbable or absent causal relation with the vaccinations. There are great differences in causality between the different event categories, but over the years very consistent (Table 12 and Figure 10). See for description and more detail the specific paragraphs under 4.8 and discussion in chapter 5.

Table 12. Causality and events of reported AEFI in 2005 (% adverse reaction)

event ⇓ causality⇒	certain	probable	possible	improbable	non classifiable	total	(% AR*)
local reaction	75	13	4	1	-	93	(99)
general illness minor	-	89	169	130	1	389	(66)
major	-	6	44	47	-	97	(52)
persistent screaming	-	41	12	5	-	58	(91)
skin symptoms	-	3	43	35	1	82	(57)
discoloured legs	-	38	16	3	-	57	(95)
faints collapse	-	50	9	16	-	75	(79)
BHS	-	1	3	2	-	6	(67)
fainting	-	48	1	3	-	52	(94)
fits convulsions	-	12	45	14	-	71	(80)
epilepsy	-	-	-	4	-	4	(0)
atypical attacks	-	7	22	12	2	43	(71)
anaphylactic shock	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	1	-	1	(0)
death	-	-	-	7	1	8	(0)
total 2005	75	308	368	280	5	1036	(73)

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

For MMR vaccination, mainly administered with other vaccines, 61% of the 315 reported adverse events were considered adverse reactions in 2005. This ranged from 53%-60% for the five previous years. For inactivated vaccines (DTP, DPTP, Hib, aK, MenC, HepB, HepA and Influenza) possible causal relation was assessed in 60% of the reports. Range for 2000-2004 was 72-87%.

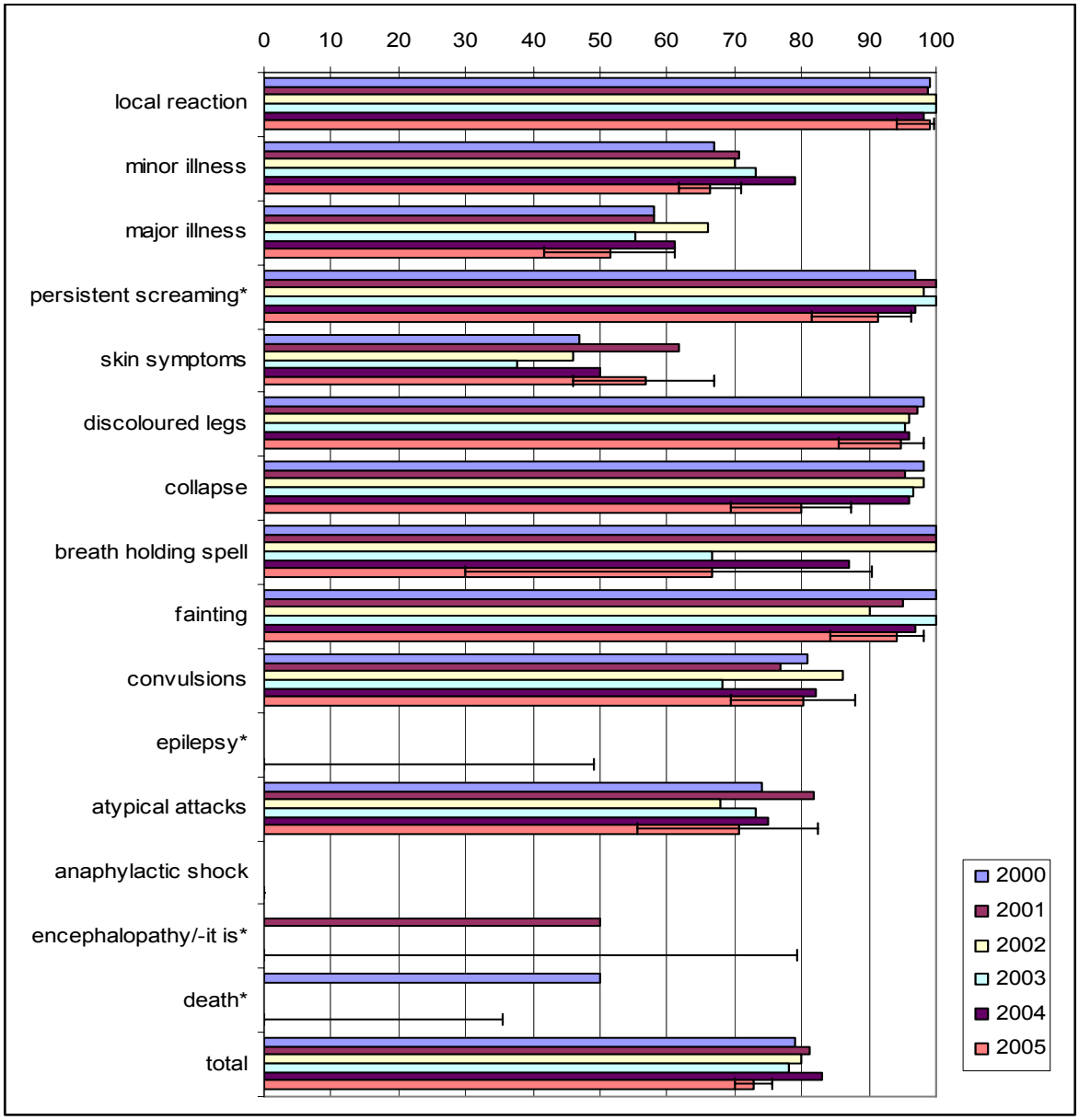


Figure 10. *Causality and events of reported AEFI in 2005 compared to 2000-2004 (with 95% confidence intervals for 2005*

* proportional with exact approximation

4.8 Categories of Adverse Events

Classification into disease groups or event categories is done after full assessment of the reported event. Some disease groups remain "empty" because no events were reported in 2005.

4.8.1 Local reactions

In 2005, 93 predominantly local reactions were reported, more frequently after DTP (48%) compared to DPTP-Hib (35%) vaccinations (Table 13). In the five previous years for local reactions there was more emphasis on the DPTP-Hib reports (63-71%). Five of the reports of

local reactions were compound, four of these with another local reaction. Eight reports were multiple. As is to be expected, nearly all reported local events were considered adverse reactions, i.e. certainly, probably or possibly causally related with the vaccination. Only one report is classified as coincidental.
The majority of the reported local reactions (73) were classified as minor reactions.
20 Reports were considered major local reactions because of size, severity, intensity or duration. Common inflammation was the most prevalent aspect in 55 reports (7 considered major). The atypical local reactions (18) concerned local rash or discoloration, possible infection, (de)pigmentation, haematoma/fibrosis, swelling, itch or pain, atypical time interval or combination of atypical symptoms. Two 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 vaccines of reported AEFI in 2005 (major events)

vaccine⇒ / event⇓	dptp hib1 (major)	dptp hib2 (major)	dptp hib3 (major)	dptp hib4 (major)	dptp hib? (major)	mmr1 menc (major)	dtp5 ak (major)	dtp6 mmr2 (major)	Other[h] (major)	2005 (major)	2004 (major)	2003 (major)	2002 (major)	2001 (major)	2000
moderate/ pronounced	4[a] (0)	3 (0)	1 (0)	8[a] (1)	-	2[g] (0)	33[c] (5)	4[e] (1)	-	55 (7)	60 (10)	75 (13)	54 (8)	34 (5)	36
absces[s]	-	1 (1)	1 (1)	4[b] (4)	-	-	2 (2)	-	5 (5)	13 (13)	14 (14)	6 (6)	8 (8)	13 (13)	9
pustule	-	-	-	-	-	1 (0)	-	-	-	1 (0)	1 (0)	0	1 (I)	3 (3)	nr
atypical reaction	2 (0)	1 (0)	2 (0)	2 (0)	-	6[f] (0)	3[d] (0)	1 (0)	1 (0)	18 (0)	29 (0)	24 (2)	31 (3)	22 (1)	25
haematoma	-	-	-	-	-	-	-	-	-	-	2 (0)	2 (0)	2 (1)	6 (1)	nr
nodule	1 (0)	-	1 (0)	1 (0)	-	-	1 (0)	-	-	4 (0)	6 (0)	4 (0)	17 (1)	6 (2)	nr
avoidance	-	-	-	1 (0)	-	-	1 (0)	-	-	2 (0)	17 (1)	12 (2)	7 (0)	6 (0)	5
total (major event)	7 (0)	5 (1)	5 (1)	16 (5)	-	9 (0)	40 (7)	5 (1)	6 (5)	93 (20)	129 (25)	123 (23)	120 (22)	90 (25)	75 (21)

[a] = once with HepB
[b] = once with MenC
[c] = once DPTP instead of DTP and aK, eight times aK only and once only DTP
[d] = once only aK
[e] = once influenza
[f] = once MMR only
[g] = once MenC only
[h] = all BCG
nr = not recorded

Nine of the 13 abscesses were drained surgically; two drained spontaneously and twice we do not know. To our information seven times cultures were taken, with four positive for Streptococcus Group A, one for Pneumococcus. Two cultures remained negative. No faulty procedures were detected.

4.8.2 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 389 children the event was considered minor illness in 2005. Of these reports 34% were considered to have improbable causal relation with the vaccination. Range for 2000-2004 is 21-33%. See Table 14 and Figure 10.

60% of reported events concerned the scheduled DPTP-Hib vaccinations. This is much lower than previous years. Range 2000-2004 is 74-90%.

Table 14. Minor illness and vaccines of reported AEFI in 2000-2005

scheduled vaccine⇓	2000	2001	2002	2003	2004	2005	(%AR*)
dptp-hib1	120	158	141	153	244	88	(73)
dptp-hib2	53	65	72	73	111	52	(79)
dptp-hib3	45	56	41	52	104	42	(57)
dptp-hib4	55	63	58	65	109	49	(61)
dptp-hib?	1	1	3	2	1	2	(50)
dptp-hib4+mmr1	2	3	3	1	1	-	-
mmr1+menC	54	63	51	78	90	104	(65)
dtp5+aK	13	16	20	11	26	28	(43)
dtp6+mmr2	23	15	8	8	14	22	(77)
menC	-	-	17	14	4	1	(0)
other	-	7	3	4	0	1	(100)
total	366	447	417	460	704	389	(66)

* percentage AEFI considered adverse reactions

Only very few times a definite diagnosis was possible; mostly working diagnoses were used. These are listed in Table 15.

Fever is the most prominent symptom in 120 reports, 95 times considered possibly causally related. Of the other (working) diagnoses, in 157 reports fever was an important accompanying symptom. Crying was the main feature in 57 reports predominantly following the first two vaccinations. These numbers are in line with 2000-2003, but much lower than in 2004. Pallor and/or cyanosis (20) and myoclonics (5) are less frequently reported than in previous years.

For the other working diagnoses numbers remained more or less the same over the last years. See for further symptoms and causality Table 15.

Table 15. Main (working) diagnosis or symptom in category of minor illness of reported AEFI in 2000-2005 (with number of adverse reactions)

symptom or diagnosis	2000	2001	2002	2003	2004	2005	AR*	symptom or diagnosis	2000	2001	2002	2003	2004	2005	AR*
fever	71	87	70	100	212	120	95	pallor and/or cyanosis	52	77	79	89	83	20	19
low temperature	1	5	2	2	2	6	4	abnormal liver enzymes	-	1	1	1	1	-	-
crying	42	51	51	59	157	57	48	rash (illness)/petechien	22	25	21	37	34	38	9
groaning	1	1	1	-	2	-	-	vaccinitis	17	21	20	31	31	39	39
irritability	5	5	4	-	6	7	3	parotitis	5	2	3	-	2	2	0
meningismus	-	3	1	-	-	-	-	infectious disease	3	2	1	2	2	4	0
hypertonia	1	1	1	2	3	-	-	swelling face/hands/feet/?	5	6	4	3	8	3	2
myoclonics	21	20	16	21	26	5	4	lymphadenopathy	4	3	2	1	-	3	2
chills	10	14	12	18	20	2	2	arthralgia/arthritis/coxitis/ limping/falling/disbalance/ pain in limbs	3	6	6	8	6	18	10
bulging fontanel	-	1	-	2	1	1	0	allergy/atopy	2	1	2	1	-	-	-
head circumference ⇑ ⇑	-	-	1	-	1	-	-	feeding problems	4	8	4	1	2	2	1
listlessness/fatigue	5	3	4	7	-	-	-	anaemia	-	-	1	-	1	-	-
drowsiness	4	4	2	5	4	4	4	vomiting/nausea	4	6	4	4	1	-	-
prolonged/deep sleep	4	9	7	8	6	7	7	stomatitis/abscess	1	1	3	1	-	1	0
behavioural problem/-illness	10	13	19	6	12	1	0	constipation/stomach-ache	2	-	2	1	-	2	1
sleeping problems	5	2	2	2	4	-	-	gastro-enteritis/diarrhoea	11	13	20	14	24	12	2
apnoea/low oxygenation	1	-	2	2	3	1	0	myoglobinuria?		2	7	-	4	-	-
asthma (attack)/cara	4	7	1	2	-	-	-	epidiydimitis/urinary tract infection/haematuria	2	1	1	-	1	1	0
airway infection	10	9	12	8	13	13	0	epistaxis	1	1	-	-	-	-	-
cough	7	4	6	4	4	1	0	headache/migraine/ dizziness	-	2	4	4	3	3	2
dyspnoea/wheezing /hyperventilation	8	4	2	3	6	3	2	eye turn/nystagmus/ squint/ anisocoria/abducensparesis /conjunctivitis/photophobia	2	3	4	1	2	3	0
pseudocroup	2	2	1	-	-	1	0	heart murmur/arrhythmia	-	-	-	1	1	1	0
tonsillitis/cold	1	3	-	-	2	-	-	lying still/frozen	8	9	6	4	10	-	-
otitis	6	2	1	3	-	3	0	undefined transient episode	-	3	1	-	1	-	-
growth disturbance	-	-	-	-	-	2	0	sundries	6	4	3	2	3	3	2
								total minor events	366	447	417	460	704	389	258

* number of adverse reactions

Major general illness

Major general illness was recorded 97 times in 2005 (range 2000-2004 74-197). Overall, 50 events were considered adverse reactions (52%). In 2000-2004 this percentage ranged between 54-65%. DPTP-Hib was involved in 46% of reported events. Compared to previous years the share of the DPTP-Hib doses has decreased. See also Table 16.

Table 16. Major illness and vaccines of reported AEFI in 2000-2005

scheduled vaccine⇓	2000	2001	2002	2003	2004	2005	(%AR*)
dptp-hib1	18	11	14	16	26	8	(13)
dptp-hib2	11	6	12	16	21	14	(50)
dptp-hib3	14	13	17	8	23	13	(38)
dptp-hib4	24	19	26	28	67	10	(70)
dptp-hib?	1	0	0	0	1	0	(0)
mmr1+menC	34	20	30	28	37	45	(62)
dtp5+aK	4	0	6	8	4	1	(100)
dtp6+mmr2	0	1	3	3	5	4	(25)
menC	0	0	3	10	10	2	(0)
other	0	2	1	2	0	0	-
total	106	74	112	119	194	97	(52)

* percentage AEFI considered adverse reactions

MMR was involved in 50 reports with in 29 cases assessed causality (58%, range for 2000-2004 was 29-66%); one of these events was attributable to another vaccine given simultaneously. For other vaccines or combinations 45 (46%) reported events were considered to be possible adverse reactions. The range for 2000-2004 was 38%-69%.

*Table 17. Major illness and vaccines of reported AEFI in 2005 (*adverse reactions)*

diagnosis⇓ vaccine⇒	dptp hib1	dptp hib2	dptp hib3	dptp hib4	mmr1 menC	dtp5 aK	dtp6 mmr2	menC	total (AR*)
very high fever (≥ 40.5°C)	-	7	6[a]	9[a]	14[b]	1	-	-	37 (28)
chills/myoclonics	-	-	-	-	1	-	-	-	1 (1)
dehydration /gastro-enteritis	-	-	1[a]	-	1	-	-	-	2 (0)
pneumonia/bronchiolitis/respiratory infection	2	2	-	1	4	-	-	-	9 (0)
apneu	1	-	-	-	-	-	-	-	1 (1)
meningitis	1	-	2[a]	-	2	-	-	-	5 (0)
vaccinitis/rash illness	-	1	-	-	12[d]	-	-	-	13 (12)
cardiomyopathy/myocarditis	1	-	-	-	-	-	-	-	1 (0)
arthritis/osteomyelitis	-	1	1	-	2	-	-	-	4 (3)
lymphadenitis colli/abcess	-	-	-	-	1	-	-	-	1 (0)
ITP	-	1	-	-	5[c]	-	1	-	7 (5)
Kawasaki	-	-	2	-	-	-	-	-	2 (0)
anaphylaxis	1	-	-	-	-	-	-	-	1 (0)
diabetes mellitus	-	-	-	-	-	-	-	1	1 (0)
retardation/autism	2[e]	1	1	-	3[f]	-	-	-	7 (0)
epididymitis	-	-	-	-	-	-	1[g]	-	1 (0)
facial paralysis	-	-	-	-	-	-	1	1	2 (0)
neuroblastoma	-	1	-	-	-	-	-	-	1 (0)
hallucinations	-	-	-	-	-	-	1	-	1 (0)
total 2005 (adverse reactions)	8	14	13	10	45	1	4	2	97 (50)

[a] = once with HepB
[b] = three times MMR0 only
[c] = once MMR0, all without MenC
[d] = once MMR0 only
[e] = once DPTP with MMR0
[f] = twice MMR only
[g] =once MMR only

Very high fever (≥40.5°C) was the working diagnosis in 37 cases, compared to 38-123 in 2000-2004. In 70% of these cases the fever was causally related to the vaccination. In the other events in this category very high fever was present in 17 cases. These included the cases with vaccinitis/rash illness, one case of meningitis, three cases of lower airway infection and once possible chills. ITP (Idiopathic Thrombocytopenic Purpura) was reported seven times. Of the six ITP cases following MMR1 four were considered possibly causally related. The reported ITP following DPTP-Hib vaccine was also considered to be possibly causally related. We received one report of anaphylaxis after the first DPTP-Hib vaccination. Twelve days after vaccination the child, known to have cow milk intolerance, got ill after milk products; there were no signs of shock. There was no causal relation with the vaccination. See for more information Table 17 and 18.

Table 18. Major illness and causal relation of reported AEFI in 2005

diagnosis⇓ causality⇒	certain	probable	possible	improbable	unclassifiable	total (%AR)
very high fever (≥ 40.5°C)	-	6	22	9	-	37 (76)
chills/myoclonics	-	-	1	-	-	1 (100)
dehydration /gastro-enteritis	-	-	-	2	-	2 (0)
pneumonia/bronchiolitis/respiratory infection	-	-	-	6	-	6 (0)
apneu	-	-	1	-	-	1 (100)
meningitis	-	-	-	5	-	5 (0)
vaccinitis/rash illness	-	-	12	1	-	13 (92)
cardiomyopathy/myocarditis	-	-	-	1	-	1 (0)
arthritis/osteomyelitis	-	-	3	1	-	4 (75)
lymphadenitis colli/abcess	-	-	-	1	-	1 (0)
ITP	-	-	5	2	-	7 (71)
Kawasaki	-	-	-	2	-	2 (0)
anaphylaxis	-	-	-	1	-	1 (0)
diabetes mellitus	-	-	-	1	-	1 (0)
retardation/autism	-	-	-	7	-	7 (0)
epididymitis	-	-	-	1	-	1 (0)
facial paralysis	-	-	-	2	-	2 (0)
neuroblastoma	-	-	-	1	-	1 (0)
hallucinations	-	-	-	1	-	1 (0)
total 2005	-	6	44	47	-	97 (52)

4.8.3 Persistent Screaming

In 2005, 58 children with persistent screaming were reported (range for 2000-2004 is 39-133). Three of the reported children had fever ≥ 40.5ºC and are listed also under major illness. 17 reports were multiple, twelve with persistent screaming after subsequent vaccinations. Reported persistent screaming appears to be again age/dose dependent, as has been noticed in former years (see Table 8). Additional symptoms were pain and swelling at the injection site, restlessness, pallor, myoclonic jerks and fever. 22 parents gave suppositories, 15 contacted the GP and two children visited the emergency room. In all but

five cases the event was considered to be causally related with the vaccinations (Table 12 and Figure 10).

4.8.4 General skin manifestations

In 2005 skin symptoms were the main or only feature in 82 reports. In 2000-2004 this ranged from 73-106. Ten reports were multiple. The percentage of reports considered adverse reactions was 57% (range 2000-2004 is 38%-63%). See Table 12 and 19.

Table 19. Skin symptoms and vaccines of reported AEFI in 2005 (adverse reactions)

vaccine⇒ / symptoms⇓	dptp hib1	dptp hib2	dptp hib3	dptp hib4	dptp hib?	mmr1 menc	dtp5 ak	dtp6 mmr2	menc	other	total (AR*)
angio-oedema/swelling	2[a]	3	1	1	-	3[b]	-	-	-	-	10 (7)
exanthema	8[a]	6[c]	4[a]	5[a]	-	19[e]	3[d]	1	-	-	46 (23)
granuloma annulare	-	-	-	-	1	-	-	-	-	-	1 (0)
urticaria	-	-	-	2	-	2[f]	1	2	-	-	7 (5)
eczema (increase)	4[a]	4[a]	5	2	-	-	1	-	-	-	16 (9)
petechiae /purpura	-	-	-	-	-	-	-	-	1	1[g]	2 (2)
total 2005	14	13	10	10	1	24	5	3	1	1	82 (46)

*= number of AEFI considered adverse reactions
[a] = once with HepB
[b] = once MMR with Hib
[c] = once DPTP only
[d] = twice aK only
[e] = once MMR0 only, five times MMR1 only of which two times with DPTP-Hib
[f] = once MMR only
[g] = HepA

All reports were considered minor events.
Exanthema, (increased) eczema and angio-oedema/swelling were the most frequent symptoms, amounting to 88%. Seven times urticaria were reported, once also with angio-oedema. Three reported children had petechial rash on upper body and/or face, one accompanied by swelling and booked under that symptom. Children with petechiae on the legs only are categorised under discoloured legs.
27 Cases concerned MMR, 22 times combined with Hib, MenC or DTP. In 59% there was a possible causal relation with MMR (range 35-77% for 2000-2004). For the inactivated vaccines or combinations, possible causal relation was assessed in 38 out of 77 events, 49% within the range for the five previous years 32-57%. See table 20.

Table 20. Skin symptoms and causal relation of reported AEFI in 2005

causality⇒ / symptom⇓	certain	probable	possible	improbable	unclassifiable	total	(%AR*)
angio-oedema/swelling	-	-	7	3	-	10	(70)
exanthema	-	2	21	23	-	46	(50)
granuloma annulare	-	-	-	-	1	1	(0)
urticaria	-	1	4	2	-	7	(71)
eczema (increase)	-	-	9	7	-	16	(56)
petechiae /purpura	-	-	2	-	-	2	(100)
total 2005	-	3	43	35	1	82	(57)

* percentage of AEFI considered adverse reactions

4.8.5 Discoloured legs

Starting from 1995, discoloured legs are listed in a separate category, subdivided in blue, red or purple legs with diffuse or patchy discoloration, with or without petechial rash. Leg petechiae without noted discoloration are also grouped in this category. Since 2001 also swollen limbs with or without discoloration after the fifth dose of DTP and aK are included. In 2005, 57 reports were received, a sharp decrease compared to previous years (Table 21; range 2000-2004 126-279). Five reports were compound. These children had also collapse and are listed in both respective subcategories. 14 Children had multiple reports of which 11 had recurrent discoloured legs and/or petechiae after subsequent vaccinations.
Five reports were considered to be blue legs (4 double-sided), 26 red legs (5 double-sided) and 8 purple legs (6 double-sided). In total, 20 reported leg petechiae, with or without prior discoloration.
Like before, reported discoloured legs occurred frequently after the first and second DPTP-Hib vaccinations (53%), but this share has decreased compared to 2000-2004 (72-79%). Causal relation with the vaccines was inferred in all but three cases. See Table 12 and Figure 10.

Table 21. Discoloured legs and vaccines of reported AEFI in 2005

vaccine⇒ symptoms⇓	dptp hib1	dptp hib2	dtpt hib3	dptp hib4	mmr1 menc	dtp5 ak	dtp6 mmr2	petechiae	total 2005	2004	2003	2002	2001	2000
blue legs	3[a]	2	-	-	-	-	-	0	5	36	29	26	31	23
red legs	2	5	8[a]	-	1	9[b]	1	4	26	130	51	40	63	46
purple legs	2	5[a]	-	-	-	1	-	1	8	69	24	43	56	47
petechiae only	3	7	4	1	-	-	-	15	15	40	26	23	22	9
swollen limb	1	-	-	-	-	1	1	0	3	4	4	5	3	nr
total	11	19	12	1	1	11	2	20	57	279	134	137	175	126

[a] = once with HepB
[b] = once DPTP and twice aK only

4.8.6 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 2005

vaccine⇒ event⇓	dptp hib1	dptp hib2	dptp hib3	dptp hib4	mmr1 menc	dtp5 aK	dtp6 mmr2	total 2005	2004	2003	2002	2001	2000
collapse	28[b]	27	10[a]	6	4	-	-	75	318	210	270	268	221
bhs	1	2	2	1	-	-	-	6	23	9	8	5	5
fainting	-	-	-	-	1	25[d]	26[c]	52	37	25	19	20	13
total	29	29	12	7	5	25	26	133	378	244	297	293	239

[a] = twice with HepB and twice Hib only
[b] = three times with HepB
[c] = once DTP and MMR
[d] = twice aK only

In 2005 collapse was reported in 75 cases. This is a sharp decrease in numbers compared to previous years. In 37% of cases collapse occurred after the first DPTP-Hib vaccination. In 2005 the number of collapse after DPTP-Hib2 is equal to DPTP-Hib1. In former years these numbers diminished with dose number and age. [39,47,50] In 2005, 10 children were reported with recurrent collapse time spaced after the same vaccination, and 10 times a collapse reaction after subsequent vaccinations. In 16 reports the event was assessed as not related because of the too long time interval and/or other causes (range 4-14 for 2000-2004). BHS occurred six times; the children turned blue, after stopping to breathe in expiration when crying vehemently or after other stimuli, with a very short phase of diminished responsiveness and no limpness or pallor. Fainting in older children was reported 52 times, considerably more than the five previous years.
See also Tables 11 and 12 and Figures 9 and 10 for sex distribution and causality and discussion in chapter 6.

4.8.7 Fits

Epileptic seizures and (febrile) convulsions are categorised 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 (65 out of 71), occurring predominantly after the fourth DPTP-Hib (15) and MMR1/MenC (44) vaccinations. For MMR this means an increase and for DPTP-Hib4 a decrease, compared to previous years. In 55 of these the fever was possibly caused by the vaccination and therefore these convulsions were considered adverse reactions. 10 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 12.

Table 23. Fits and vaccines of reported AEFI in 2005

vaccine⇒ / event ⇓	dptp hib1	dptp hib2	dptp hib3	dptp hib4	mmr1 menc	dtp aK	dtp6 mmr2	menc	total 2005	2004	2003	2002	2001	2000
febrile convulsion simple	-	-	1	9	23[c]	1[d]	-	-	34	45	28	22	26	29
complex	-	2	-	5	15[b]	1	-	1	24	32	23	20	21	26
tonic	-	-	-	1	1	-	-	-	2	5	2	-	2	1
atypical/not specified	-	-	-	-	5	-	-	-	5	8	11	3	2	3
non febrile convulsion	-	2	-	1[a]	2[b]	1	-	-	6	8	6	-	5	4
epilepsy	1	-	2	1	-	-	-	-	4	9	5	5	10	7
atypical attack	9[e]	3	4	7[f]	19[g]	1[d]	-	-	43	104	57	41	55	42
total	10	7	7	24	65	4	-	1	118	211	132	91	121	112

[a] = only Hib
[b] = once MMR only
[c] = four times MMR only
[d] = only DTP
[e] = twice with HepB
[f] = once with HepB
[g] = once MMR0

14 Children had fever ≥ 40.5°C, but these were not listed under major illness since the fever was considered part of the event. In all but two, this very high fever occurred in the one year-olds. See Table 11 for sex distribution and Table 10 for level of intervention.
Six non-febrile convulsions were reported. Two of these were considered possibly provoked by the vaccination, the other four were considered chance occurrences.
Four children with epilepsy were reported, of whom two had (possible) West syndrome. In none of these children (fever caused by) the vaccine was regarded as trigger.
In 2005 atypical attacks were recorded 43 times, with in 29 cases 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 23). Reported atypical attacks at the younger ages were less frequently accompanied by fever than at later doses/older ages. Six children had fever of $\geq$40.5°C, all considered causally related to the vaccination.
In 2005 MMR was involved in 65 reports, 54 times with simultaneous MenC. Causality of the event with MMR was assumed in 58 cases. Thus there was imputed causal relation of the fits with MMR in 89% of the reports (range 58-80% for 2000-2004). For the other vaccines 37% of the reported events were considered adverse reactions. Range for 2000-2004 is 46%-78%.

4.8.8 Encephalopathy/encephalitis

The only event reported in 2005 listed in this category was considered a chance occurrence and not induced or aggravated by the vaccination.
The child cried a lot during the first months of life and vomited frequently after feeding. The day after the third DPTP-Hib and second HepB vaccination the child vomited, became hypertonic and subsequently limp and unconscious. The GP started resuscitation. There were clinical signs of elevated intracranial pressure. Treatment with antibiotics and corticosteroids was started on suspicion of meningitis. Investigation revealed diffuse cerebral damage and loss of brain-tissue. In both eyes there were preretinal haemorrhages. Neurological there was decortication with spontaneous respiration. Shaken baby syndrome was diagnosed.

4.8.9 Anaphylactic shock

There were no reports on anaphylactic shock in 2005. As a matter of fact, we have never received notification of anaphylactic shock with inferred causality and/or appropriate time interval since the surveillance system was installed.

4.8.10 Death

In 2005, eight children who died following vaccination, were reported (Table 24). Three late reports were included. These resulted from the new collaboration with the Netherlands Paediatric Surveillance System for SIDS (LWW). The reports concerned five girls and three boys. See the case histories below. Four times autopsy was performed, 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 not possible. In all eight cases death was not judged to be caused or hastened by the vaccination.

Table 24. Death and vaccines of reported AEFI in 2005

child	sex	age[a]	vaccines	time interval illness	time interval death	symptoms/diagnosis	causality[b]	autopsy
A	f	14m	mmr1+menc	8d	8d	listless, low-grade fever, crying, clinical SIDS	no	no
B	f	5m	dptp2+hib2	7d	11d	cough, listless, clinical SIDS	no	no
C	f	2m	dptp1+hib1	-	40h	facial and cardiac anomalies, megalencephaly with degenerative changes in grey and white matter	no	yes
D	m	2m	dptp1+hib1	-	70h	SIDS	no	yes
E	m	15m	mmr1+menc	9d	9.5d	fever, listless, viral infection in heart and lungs	no	yes
F	m	2m	dptp-hib1 +hepb1	-	1.5-2d	clinical SIDS	no	no
G	f	2m	dptp-hib1	-	<1d	SIDS	no	yes
H	f	15m	mmr1+menc	4d	5d	common cold, listless, clinical SIDS	no	no

[a] yes=inferred causality certain, probable or possible; no= inferred causality improbable or absent; nc= non-classifiable

[b] age at vaccination

Child A

A girl of 14 months old got her first MMR and MenC vaccinations. Eight days after the vaccinations she became listless with poor appetite, had low grade fever and cried a lot. The parents put her to bed. One hour later the mother found her lying in prone position with her head against the edge. She had vomited, had stopped breathing and felt cold. Resuscitation was not successful.

Child B

A girl of 5 months old received the third dose of DPTP and Hib. The day of vaccination she developed fever. The next day she was well again. She frequently had a cold and coughed regularly. One week after the vaccination she was listless and developed a cough for which she was prescribed deptropin mixture. Eleven days after the vaccination she was put to bed and the parents found her dead 2.5 hours later.

Child C

A girl of 2 months of age was vaccinated with the first DPTP and Hib. She already had a common cold. That day she developed fever, which had disappeared the following morning. Forty hours after vaccination when she cried, the parents took her in bed. Thirty minutes later she was found dead. Short after birth the child was examined because of feeding problems and facial dysmorphisms. Autopsy revealed also several cardiac anomalies and megalencephaly with degenerative changes in grey and white matter, but no definite indication of cause of death.

Child D

A boy of 2 months of age got the first DPTP and Hib vaccinations. During that day he was crying and had fever. The next day everything was all right again. Seventy hours after the vaccination he was found dead lying in bed with his parents. Autopsy revealed no cause of death.

Child E

A boy of 15 months old received the first MMR and MenC vaccinations. Nine days later he got fever and was listless. Parents brought him to bed for the night. The next morning they found him lifeless, lying on his belly. Autopsy revealed signs of a viral infection in heart and lungs. No pathogen was isolated.

Child F

A boy of two months old got his first DPTP-Hib and HepB vaccinations. He already had a cold. That day he slept a lot and drank less. This improved the next day and he drank his evening and night feeding normally. He usually slept in the parents' bed and was found dead and cold the morning, two days after the vaccination. Cultures of blood, CSF were negative. Nasal and anal swabs gave no isolates. No autopsy was performed.

Child G

A girl of two months received her first DPTP-Hib vaccination. That day she remained well. As usual she slept in bed with the parents and was found dead the next morning. Full post mortem did not reveal a cause of death. The diagnosis was SIDS with several other risk factors for SIDS present.

Child H

A girl of 15 months old received MMR1 and MenC. Five days after the vaccinations she developed a common cold and was somewhat listless. She was put to bed at 17.30 hr as usual. Two and half hours later she was found in prone position. Resuscitation was in vain. Nasopharyngeal culture was positive for RSV. The blood and liquor culture was contaminated with Streptococcus Salivarius. Urine analysis and babygram were normal. No autopsy was performed.

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 increased attention 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 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 distortion. Therefore the representativeness of data on AEFI presented here, will be discussed.

The year under report was given special attention because of the change to DPTP-Hib vaccine with an acellular pertussiscomponent for infants in January 2005. The Minister of Health thus followed the advice of the GR of April 2004. GR assumed that poor effectiveness of the whole cell vaccine caused the high incidence of pertussis in the Netherlands. GR stressed also the reactogenicity of the formerly used vaccine. [1] Since January 2004 there had been a lot of public concern about the safety of the whole cell pertussis vaccine with repeated media attention. The GR advice added substantially to this adverse publicity. This increased attention resulted in a steep rise in the number of AEFI in 2004. However no unexpected severe or new adverse events were unveiled. [50]

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 decrease in number of reports and the different aspects of the nature of the reported adverse events in 2005.
We will discuss the safety of the vaccination programme in the light of the here presented results of the current enhanced passive surveillance system (and with regard to the literature) and consider future approaches.

5.1 Number of Reports

In 2005 the number of reports decreased to half the number of 2004. This year has been considered an outlier because of the influence of the public unrest on the numbers. Compared to the more stable years 2000-2003 there is also a reduction of approximately one quarter.

This is in line with expectation since acellular pertussis vaccines are known to have a more favourable safety profile, both for the more common as for the more severe adverse events.[63,64,65]

The number of multiple and compound reports decreased to the level before 2004. There has always been fluctuation in these numbers.
However signals have reached us that active follow up of possible AEFI at the clinics has diminished also. This was driven by the expectancy of clinic staff that this new vaccine "does not have any side-effects at all". We have tried to repair this in contacts with the clinics.
We have to bear in mind that this report does not cover a full year use of acellular DPTP-Hib vaccine.
Ongoing surveillance is necessary to confirm at which level these numbers will stabilise.

5.1.1 Distribution over Vaccines and Dose

The decrease in reports was mainly due to the DPTP-Hib vaccinations. The share of reports concerning DPTP-Hib was 57%, compared to 81% in 2004 and 78% on average for 2000-2003. This diminished relative share of DPTP-Hib reports is somewhat confounded by simultaneous increase in absolute numbers of reports of other vaccines. The relative frequency within the four DPTP-Hib doses changed again to less predominance of the first dose (35% in 2005, 42% in 2004 and 47% on average in 2000-2003). The first vaccination with DPTP-Hib always has a higher number of reports than the later doses. To some extent this will be because of 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.
In the first months of a year, events taking place at the end of the previous year are reported, in this case episodes associated with the whole cell vaccine. There was however no significant trend during the year of diminishing number of notifications. Normal seasonal fluctuation was applicable.
The further rise of reports following MMR1 after the inclusion of simultaneous MenC vaccination seems to be due to decreased underreporting and increased willingness to report.
Because of temporary vaccine shortage of the single acellular pertussis vaccine (aK) for the four-years-olds in the spring of 2005 approximately 50,000-100,000 children received this vaccine later in the year. This resulted in substantial increase in vaccination dates in this age group. This explains the 20 reports on single aK vaccine.
Reports following the vaccinations of the nine-year-olds are equal to 2004.
See for details the following paragraphs.

5.1.2 Distribution over Events

The decrease in reports is apparent in all event categories, except the number of reported encephalopathy and death. To get more accurate estimations on the incidence of specific

adverse events, we continued the questionnaire study of the more severe adverse events following DPTP-Hib started in December 2003 (to be reported later).
No new or unexpected events were detected in infant age groups in 2005. Remarkable however were some unusual local reactions following single acellular pertussis (aK). [66,67,68,69] This signal has been followed up by a questionnaire study in the four-year-olds in 2006. See for more details under paragraph 6.2.

5.1.3 Severity, Causality, Level of Intervention and Reporting Interval

In the current year the absolute number as well as the relative share of so called major adverse events diminished, mainly due to a decrease in DPTP-Hib reports. This is consistent with the better safety profile of the new acellular pertussis component. [63,64,65]
The percentage of all reports with assumed causality (adverse reactions) decreased to 73%, compared to 78-83% in 2000-2004. Compared with 2004 the assessed causal relation with DPTP-Hib vaccine diminished from 86% to 72%. Relatively more coincidental, unrelated events were reported than usual following DPTP-Hib. This is 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. [39,59]
Reporting coincidental events in close time relationship with vaccination also indicates good willingness to report. For the other vaccines or vaccine-combination the percentage adverse reactions was similar to previous years.
Contrary to what may have been expected, the reporting intervals for DPTP-Hib were similar in 2005 and 2004, with 27% and 28% within 28 days, respectively. If anything this doesn't point to a change in risk perception or severity of the reported events between the two years.
Percentage wise the level of medical intervention (GP, clinic and hospital visit) for DPTP-Hib was similar (approximately 45%) in 2005 and 2004. Relatively more children were admitted to hospital following DPTP-Hib in 2005 (12%) compared to 2004 (7%). However in 2005 68% of admissions were for coincidental, unrelated adverse events compared to 39% in 2004. In absolute numbers these were 46 and 48 unrelated hospitalisations respectively. The type of vaccine does not influence the risk of chance occurrences following the vaccination of course.
All the aspects in this paragraph point to fewer adverse events following acellular DPTP-Hib and also to a decreased severity of the reported adverse reactions.

5.1.4 Underreporting

Reducing underreporting is of special importance in passive surveillance systems, especially of selective underreporting. Since 1994 we continuously put extra effort into this, as has been discussed in previous annual reports[41,42,43,42,45,45,48,48,49,50]. It has been concluded that the rise in number of reports in 1994-1997 resulted mainly from this effort, with a minor influence of the introduction of a new vaccine (Hib) from July 1993 onwards. The increase in number of reports in 1998 was held to be partly due to a further decrease in underreporting, increased

apprehension or awareness, but also to an increase of real adverse reactions caused by the use of the higher potency pertussis component in the DPTP vaccine. [41] The reports of 1999 were difficult to interpret since the change in schedule did not apply to the full calendar year but only to the children born in 1999 (and after) which resulted in vaccination of an extra number of children. [42] The number of reports in 2000 was comparable to 1998, but there was a shift in reports for some age-specific adverse events, held to be due to the effect of the new schedule, with earlier start[45]. [45] The small rise in number of reported AEFI in 2001, 2002, 2003 may be partly due to a decrease in underreporting in some regions with a somewhat larger proportion of minor events in the regions with the highest increase in reporting rate, but this certainly cannot explain the total increase in numbers. [46,48] A better adherence to the accelerated schedule may be responsible for some increase in young-age specific events. In part the increase may also be the result of introduction of three new vaccines (aK, MenC and HepB for risk groups). The increase in numbers of 2004 is due to a general decrease in underreporting, induced by the adverse publicity. [50]
In the current year total number of reports has gone down significantly. This is probably due to a real decrease in actual adverse events because of a better safety profile of acellular pertussis vaccines. [63,64,65] To a small degree perhaps some underreporting based on the (wrongful) assumption of an ideal vaccine without any adverse events may play a role. However the stable rather even distribution of the reporting rates over the country suggests a satisfactory performance of the passive surveillance system.
Continued surveillance is necessary to increase our knowledge on the safety of acellular pertussis vaccine in the Netherlands. This will also shed light on the so called “honeymoon” effect. The ongoing questionnaire study on the more severe, rare events following DPTP-Hib vaccine will lead to more precise incidence estimates.

5.2 Specific Events

In addition to what is said in the above paragraphs some specific adverse events will be discussed below.

5.2.1 Local reactions

Since the introduction of aK at four years of age for the birth cohort 1998 and later the number of local reactions after simultaneous administered DTP and aK increased, most prominently in 2003 and the year under report. Remarkable was the type, extension and the long time interval with vaccination, also in the group that received acellular pertussis only. This may be partly due to decreased underreporting, but is suspect for a true increase in local reactions after pertussis booster vaccinations. [66,67,68,69] In 2006 we performed a questionnaire study on adverse events after DTP and aK to follow up this signal.

5.2.2 Minor illness

The number of reports in the current year in this category returned to the level before 2004. 197 (51%) of these reports involve fever <40.5°C, crying and pallor. Three quarters (150) concerned DPTP-Hib, of which 114 with acellular vaccine. In 2000-2004 the numbers of reports with working diagnosis fever, pallor, cyanosis or crying increased from 163 till 452. These reports concerned DPTP-Hib in up to 90%.
Fever, crying and pallor are acknowledged common adverse events following DPTP-Hib vaccination. Accurate estimates are rare in literature. In the Swedish pertussis trials Olin found 4.4% pallor following the first dose of whole cell pertussis vaccine as opposed to 0.4% for acellular pertussis vaccine. [65] In a questionnaire study we found up to 18% reported pallor following the first dose of whole cell DPTP-Hib. Especially pallor, mainly occurring after DPTP-Hib, is significantly less reported than in previous years. For fever following acellular pertussis vaccine the numbers also went down. For crying this was less obvious. Results of the questionnaire study for acellular DPTP-Hib are not available yet. We must bear in mind that this annual report does not cover a full year of use of acellular DPTP-Hib. The trends are an indication however of a lower incidence rate of these common adverse events.

5.2.3 Very high fever

Fever is a very unspecific symptom of very many medical conditions. It is also an acknowledged adverse event following immunisation. In all pre registration trials this event is covered. The Brighton Collaboration covered this event in the first series of six case definitions with stipulations how to report in increments of .5 degrees centigrade (Celsius). [70] We have registered events under very high fever (≥ 40.5°C) only if the event was not part of another disease entity.
This year 54 events were reported, involving very high fever, of which 40 in the one-year-olds (30 times MMR1 and 10 times DPTP-Hib4). Compared to previous years the number of very high fever following DPTP-Hib4 was considerably lower. This is a first indication of the lower reactogenicity of acellular pertussis vaccines. Longer passive follow up is necessary. More precise estimates will come from the current questionnaire survey.

5.2.4 Persistent screaming

The number of reports of persistent screaming returned to levels of before 2004, in which year there was a tremendous increase, due to adverse publicity. There has always been a known underreporting of persistent screaming. Exact incidence rates are difficult to compare/obtain, because of different case definitions. [71,72,73,74] 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. [75] We register the duration however in order to be able to pool or compare results.

Best incidence estimates from our questionnaire study are 0.5%-1.0% following DPTP-Hib1 for validated reports with the same case definition. In the literature, estimates of persistent screaming are 1-10 per 1000 children depending on case definition and age involved. [75,76] For the acellular pertussis vaccine in the Dutch situation we expect results from the current questionnaire study.

5.2.5 Collapse

Since 1999 the numbers of reports of collapse reactions have gone up, with in 2000 and 2001 some further increase, and since then stabilisation. The current year shows a decrease of collapse reactions, most prominent after the first dose (27; range 2000-2004 is 147-198). This may be an indication of a lower incidence rate of collapse following acellular pertussis vaccines. However some other factors may play a role. There seems to be a shift to a later age of the first DPTP-Hib dose, with only 33% within 9 weeks, compared to 42% on average in 2000-2004. Age is an important risk factor of collapse following DPTP-Hib. Also we received a signal from some regions that collapse and discoloured legs were reported less consistently. Denominators, the numbers of vaccinated infants, are not known yet. The birth cohorts of 2004 and 2005 are relatively small. We will go into this in the following years.
In the passive surveillance system the incidence rate of collapse following the first dose of whole cell pertussis vaccine was 1 in 1000 children. The questionnaire study showed that the level of underreporting was satisfactorily low; maximum incidence estimate is this study was 1.2-1000 (95%CI 0.4-2.8).

5.2.6 Discoloured legs

Numbers of reported discoloured legs have decreased greatly compared to 2004 and 2003. The same comments as given for collapse apply here. The decrease may be an indication of a lower incidence rate of discoloured legs following acellular pertussis vaccines. But also this may be influenced by a shift in the age of vaccination, lower denominators of vaccinated infants and some increase in underreporting. Discoloured legs are not described in literature. The questionnaire study of 2004 did not supply incidence rate estimate in de Netherlands. We are working on a suitable case definition, extracted from the clinical symptoms of all reported cases since 1994. This case definition will serve for future studies.
We will look in our reports for the newly reported adverse event with a swollen limb or extensive limp swelling (ELS, mainly after subsequent doses of aK vaccine in other countries); they may be filed in the two event categories, e.g. discoloured leg syndrome or local reactions. Internationally we will have to work on uniform case definition for this “so called” ELS. [68,69]

5.2.7 Convulsions and Atypical Attacks

The number of (classic) febrile convulsions was significantly lower than in previous years. Most reported febrile convulsions occur in the one-year-olds. The number following MMR and MenC is equal to 2004. For DPTP-Hib4 the number is lower. This may be because of the

lower rate of fever following acellular pertussis vaccines. [63,64,65] Irrespective of assessed causality for DPTP-Hib4 the incidence rate is 0.8 (95%CI 0.4-1.3) per 10,000 vaccinations. This is a little lower than previous estimates following whole cell pertussis vaccine. [77,78] In the questionnaire study in 2004 only one febrile convulsion followed DPTP-Hib4 (2.8 per 10,000 children; 95%CI 0.1-15.5). In the following years with only acellular pertussis vaccine in use, the performance of the acellular pertussis vaccine will become clearer.
The number of reported atypical attacks was substantially lower than 2004 but again in range with 2000-2003. Numbers fluctuate considerably 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 have come up. The numbers in this subgroup are (very much) dependent on completeness of information. Thus, in different years transfer to and from other event categories varies. If planning and priorities permit, we plan to look into the phenomenon of atypical attack in more detail.

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. [79,80] Despite the fact that based on scientific evidence renowned (groups of) scientists have refuted these alleged associations, especially in the United Kingdom and the Republic of Ireland the vaccination coverage dropped considerably. [81,82] 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. [83,84] Studies refuting the causal relation of encephalopathy or retardation with pertussis vaccinations have been published earlier and confirmed lately. [85] No new signals have emerged in 2005.

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 done on the aetiology of epilepsies. [78] However, it may not be possible to exclude this

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. [86] However, the age at which West syndrome occurs coincides with the vaccination schedule. The fact that in the current year the reported number of epilepsy is equal to previous years is a further indication of non causality.

5.2.10 Death

This year eight children were reported that died some time after immunisations. Three of the children were late reports coming from the collaboration with LWW. This collaboration is formed to increase capture of both systems.
The number of reports in this category is in line with expectations considering the background rate. In none of the children causality with the given vaccinations was considered to be present, after thorough evaluation. Neither was there considered indirect causality, with delay in treatment or aggravation of symptoms because of the vaccination. In four children a full post mortem has not been performed leaving room for uncertainty and speculations. It should be stressed that full post mortem investigations of children is strongly advisable, even if underlying severe conditions are present. This is beneficial for both the individual child and its distressed parents, and on population level.
Systematic studies and evaluation of the Institute of Medicine have shown infant death to be unrelated to childhood vaccinations. [87] 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 done 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. [19,20,88,89,90] 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 (24-hr) central telephone information and consultation service for professionals is a most important and efficient tool in adverse events reporting. [91] 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. [49,92] 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. [93,94,95,96] Of course, after vaccination does not mean caused by vaccination. The RIVM expert panel will continue the former GR activities of broader scientific assessment of selected cases. 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.[97,98,99] 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. [100] 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. [16,96] 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, there where they are in actual use.

5.3.2 Passive Surveillance versus Active Surveillance

The current enhanced passive surveillance system will 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. 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). [101,102,103] 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. [104] These registers should also qualify for safety surveillance. In the Netherlands the new centralised vaccination database fulfils these criteria.

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. West syndrome and other severe epilepsies of infancy may be the first candidates. 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. [105] 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. Reporters prefer however the reporting by telephone as less time consuming and of advantage because of the possible consultation. For data quality reports received by telephone are superior and efficient since they allow necessary supplementation and validation. 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. We have noticed the importance of stressing repeatedly the need for adherence to the wide reporting criteria. In the year under report in some regions collapse and discoloured legs e.g. were reported less. Although these events pose no contraindication and the clinic knows who to manage the adverse events, they still should be reported.
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. [106,107,108,109,110] 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 for too long the

vaccine was thought to be the cause of the illness. [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. [3,111,112,113,114] 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. [115]

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. [93,94,95,96] Individual continuation of the schedule depends on proper assessment. It is important for the entire population served also, as 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

2004 has shown that the enhanced passive surveillance system picked up signals of increased reports and public apprehension quickly. [116] In the year under report introduction of a new acellular DPTP-Hib vaccine yielded many questions about the safety of this unfamiliar product, resulting in reporting of relatively more coincidental adverse events. This year may be regarded as the honeymoon of the acellular DPTP-Hib vaccine. The year under report hasn't covered a full year use of acellular pertussis vaccines. Passive safety surveillance in the next years will reveal the safety profile in more detail. However frequent changes in product and additions to the schedule may impede comparisons. For some adverse events the ongoing questionnaire study will supply incidence estimates for some adverse events.
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 enough 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 2005 the number of reported events decreased significantly due to adoption of an acellular DPTP-Hib vaccine with a more favourable safety profile. Precise description of this profile is only possible after a longer surveillance period. This is hampered however, by frequent shifting to other DPTP-Hib products and expansion of the programme with pneumococcal vaccine.
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 planned database system for adverse event surveillance should 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. [117,118]
Introduction of new vaccines should be organised in a manner 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, are recommended:

- further implementation of database applications and mutual adjustment with Lareb;
- annual report on 2006;
- 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;
- continuation of active study of incidence rates of some acknowledged but not so common adverse events following DPTP-Hib and pneumococcal vaccinations;
- case only study on vaccinations and SIDS;
- active follow up of changes in the programme.

We plan to keep up a thorough high quality safety-surveillance-system and to stimulate reporting in the coming year. Thus, one can show that the vaccination programme is safe. The total of 1036 reports must be seen in relation to a total of over 1.4 million vaccination dates administered with nearly 7 million components. Therefore the vaccination programme is safe with the potential side effects far less in weight than the apparent achievements/prevented illness and complications.

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Appendix 1 Vaccination Programme 2005

STAATSTOEZICHT OP DE VOLKSGEZONDHEID

INSPECTIE VOOR DE GEZONDHEIDSZORG

Rijksvaccinatieprogramma 2005

tegen: Difterie, Kinkhoest, Tetanus, Poliomyelitis, Haemophilus influenzae type b, Hepatitis B, Bof, Mazelen, Rodehond en Meningokokken C voor de kinderen geboren in:

- 2005: DaKTP-Hib + Hep B[1]
- 2004: DaKTP-Hib + Hep B[1] + BMR + Men C
- 2001: DTP + aK
- 1996: DTP + BMR

1 Algemeen

1.1 Organisatie

De uitvoering van het Rijksvaccinatieprogramma wordt verzorgd door Thuiszorgorganisaties en GGD'en, onder verantwoordelijkheid en medisch toezicht van de Entadministraties en in overeenstemming met de richtlijnen van de Inspecteur-Generaal voor de Gezondheidszorg.

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 en onder voorwaarde dat de vaccins worden aangewend voor de uitvoering van het Rijksvaccinatieprogramma (RVP) 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.
Indien ouders kiezen voor een ander vaccin dan dat door de minister voor gebruik in het RVP is aangewezen en/of indien 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 tenminste 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).

(1) Alleen voor de in paragraaf 2 van deze circulaire omschreven doelgroepen.

Voor het afmaken van onvolledige series wordt verwezen naar Rudy Burgmeijer & Nico Bolscher *Vaccinaties bij kinderen*, vierde, geheel herziene druk, Koninklijke Van Gorcum 2002.

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 2005 vereisen de goedkeuring van de Inspecteur-Generaal voor de Gezondheidszorg.

1.8 Aanvragen extra circulaires

Exemplaren van deze circulaire kunnen worden aangevraagd bij de Inspectie voor de Gezondheidszorg, Postbus 16119, 2500 BC Den Haag, telefoon (070) 340 5536 of bij de regionale Entadministratie (zie paragraaf 8). De circulaire is ook te vinden op www.igz.nl.

2 Zuigelingen

Vaccinatieschema

- DaKTP (Difterie – Kinkhoest/acellulair vaccin – Tetanus – Poliomyelitis) -- Hib (Haemophilus influenzae type b))

Op de leeftijd van respectievelijk 2, 3 en 4 maanden wordt één DaKTP-Hib-vaccinatie gegeven. Er dient minimaal een periode van 4 weken in acht te worden genomen tussen de drie opeenvolgende vaccinaties. De vierde DaKTP-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 DaKTP-Hib-vaccinatie en de vierde DaKTP-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 DaKTP-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 DaKTP-Hib-vaccinatie. Vanaf de leeftijd van 1 jaar kan dan met één Hib-vaccinatie worden volstaan. Indien kinderen nog in aanmerking komen voor een DaKTP-vaccinatie, maar niet meer voor een Hib-vaccinatie, kan in het kader van het RVP alleen DaKTP-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:

- 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%)[2].
- Kinderen van HbsAg-positieve moeders (draagsters van het Hepatitis B virus).

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 DaKTP-Hib-vaccinatie gegeven, waarbij het Hep B-vaccin en het DaKTP-Hib-vaccin in verschillende ledematen worden toegediend.

Uitstel van de Hep B-vaccinatie is 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. Bij deze kinderen zal om die reden zo spoedig mogelijk na de geboorte Hep B-immunoglobuline toegediend worden. Verder heeft

(2) De WHO geeft een lijst van landen waar Hepatitis B laag-endemisch is (prevalentie van dragerschap < 2%), de zogenaamde negatieve landenlijst: Andorra, Australië, Bahamas, Barbados, België, Bermuda, Canada, Chili, Colombia, Costa Rica, Cuba, Cyprus, Denemarken, Duitsland, El Salvador, Estland, Finland, Frankrijk, Hongarije, Ierland, Luxemburg, Mexico, Monaco, Nederland, Nicaragua, Nieuw-Zeeland, Noorwegen, Oostenrijk, Paraguay, Peru, San Marino, Sri Lanka, Slowakije, Tsjechië, Uruguay, IJsland, Verenigd Koninkrijk, Verenigde Staten, Zweden en Zwitserland.

de minister besloten dat het kind hierna, bij voorkeur in de eerste levensweek, de eerste Hep B-vaccinatie ontvangt. Het was op het moment dat deze circulaire werd opgesteld nog niet duidelijk wanneer deze eerste Hep B-vaccinatie op t=0 landelijk zal worden ingevoerd en wie deze gaat toedienen. Er zal hierover te zijner tijd aparte berichtgeving volgen.
Vanaf 2 maanden wordt de serie Hep B-vaccinaties bij deze kinderen afgemaakt volgens het RVP schema. Omdat het hier post-expositie profylaxe betreft en geen preventie, dient het schema van 0, 2, 4 en 11 maanden strikt gevolgd te worden.

– BMR (Bof – Mazelen – Rodehond)
Op de leeftijd van 14 maanden wordt één BMR-vaccinatie gegeven.
Dosering: 0,5 ml SUBCUTAAN.

– 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 2001 geboren kinderen worden in 2005 gerevaccineerd met DTP-vaccin.
Dosering: 1 ml INTRAMUSCULAIR.

– aK (Kinkhoest – acellulair vaccin)
De in 2001 geboren kinderen worden in 2005 gerevaccineerd 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 (in de bovenarm).

Indien kinderen geen (volledige) serie DKTP-vaccinaties hebben ontvangen, dient deze serie met DaKTP-vaccin afgemaakt worden en niet met los DTP- en aK-vaccin, vanwege de hogere sterkte van de D-component in het DaKTP-vaccin.

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.

4 Schoolkinderen

Vaccinatieschema
– DTP (Difterie – Tetanus – Poliomyelitis)
De in 1996 geboren kinderen worden in 2005 gerevaccineerd met DTP-vaccin.
Dosering: 1 ml INTRAMUSCULAIR.

– BMR (Bof – Mazelen – Rodehond)
De in 1996 geboren kinderen krijgen in 2005 één 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.

Indien deze vaccinaties om een of andere reden niet simultaan kunnen worden gegeven, dienen tussen de vaccinaties de volgende intervallen aangehouden te worden:
– Na een DaKTP-Hib-vaccinatie, een DTP-vaccinatie, een Hib-vaccinatie, een Hep B-vaccinatie, een Men C-vaccinatie en/of een aK-vaccinatie dient 2 weken gewacht te worden alvorens een ander vaccin mag worden toegediend,
– Na een BMR-vaccinatie dient 4 weken gewacht te worden alvorens een ander vaccin mag worden toegediend.

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

INSPECTIE VOOR DE GEZONDHEIDSZORG

6 Bijwerkingen

Na vaccinaties kunnen bijwerkingen optreden. Meestal betreft dit lichte, veelal lokale verschijnselen. Elke bijwerking, zeker de meer ernstige, kan de vaccinatiegraad negatief beïnvloeden. Er wordt dan ook dringend verzocht elke ernstige, onverwachte of onrust veroorzakende (mogelijke) bijwerking te melden aan het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) te Bilthoven, onder vermelding van het partijnummer van het betreffende vaccin (tel. 030 274 2424; fax 030 274 4430; Email: libris@rivm.nl).

7 Vaccinatieschema per kind

Leeftijd		*Vaccinaties*
2	maanden	DaKTP-Hib-1 + Hep B-1[3]
3	maanden	DaKTP-Hib-2
4	maanden	DaKTP-Hib-3 + Hep B-2[3]
11	maanden	DaKTP-Hib-4 + Hep B-3[3]
14	maanden	BMR-1 + Men C
4	jaar	DTP-5 + aK
9	jaar	DTP-6 + BMR-2

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
Postbus 4050, 9701 EB Groningen
Telefoon 050 368 6350, Fax 050 312 2733
Email info@stenn.nl
Overijssel/Flevoland
Postbus 43, 7730 AA Ommen
Telefoon 0529 455 717, Fax 0529 455 805
Email info@entorganisatie.nl
Gelderland
Postbus 357, 6800 AJ Arnhem
Telefoon 026 442 9242, Fax 026 443 4999
Email ent@speg.nl
Utrecht/Noord-Holland
Postbus 1097, 3600 BB Maarssen
Telefoon 0346 550 040, Fax 0346 573 795
Email algemeen@entutrecht.nl
Amsterdam
Postbus 2200, 1000 CE Amsterdam
Telefoon 020 555 5460, Fax 020 555 5071
Email jgzent@gggd.amsterdam.nl
Zuid-Holland
Postbus 654, 2700 AR Zoetermeer
Telefoon 079 341 8238, Fax 079 331 5047
Email ent@reazuidholland.nl
Rotterdam
Postbus 70032, 3000 LP Rotterdam
Telefoon 010 433 9518, Fax 010 433 9652
Email ent@ggd.rotterdam.nl
Zeeland
Postbus 53, 4460 AB Goes
Telefoon 0113 224 080, Fax 0113 224 055
Email entadministratie@spkez.nl
Noord-Brabant
Postbus 8220, 5004 GD Tilburg
Telefoon 013 540 0688, Fax 013 540 0086
Email spen@peab.nl
Limburg
Postbus 5148, 6130 PC Sittard
Telefoon 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 voor Entadministraties)
Postbus 100, 3980 GB Bunnik
Telefoon 030 299 3187, Fax 030 242 0874
Email lve@entadministraties.nl

Voor achtergrondinformatie over het Rijksvaccinatieprogramma verwijs ik verder naar de website www.rijksvaccinatieprogramma.nl.

Rijksvaccinatieprogramma 2005
tegen: Difterie, Kinkhoest, Tetanus, Poliomyelitis, Haemophilus influenzae type b, Hepatitis B, Bof, Mazelen, Rodehond en Meningokokken C en voor de kinderen geboren in:

- 2005: DaKTP-Hib + Hep B[3]
- 2004: DaKTP-Hib + Hep B[1] + BMR + Men C
- 2001: DTP + aK
- 1996: DTP + BMR

Prof. dr. J.H. Kingma
Inspecteur-Generaal voor de Gezondheidszorg
Den Haag, december 2004

[3] Alleen voor de in paragraaf 2 van deze circulaire omschreven doelgroepen.

Appendix 2 Resume Product Information

Vaccines in RVP	Producer	constituents
DKTP-Hib vaccin Diphtheria, acellular Pertussis, Tetanus and inactivated Poliomyelitis vaccine mixed with conjugated Hib-vaccine 0.5 ml	GSK RVG 22123	Diphtheria-toxoid * ≥30 IE Tetanus Toxoid* ≥ 40 IE Pertussis toxoid (PT)* 25µg Filamenteuze hemagglutinine (FHA)* 25µg Pertactin* 8µg Inactivated poliovirus type 1 40 DE Inactivated poliovirus type 2 8 DE Inactivated poliovirus type 3 32 DE Haemophilus influenzae type b polysacharide** 10µg *adsorbed to aluminiumhydroxide 0.95 mg **conjugated to tetanus toxoid and adsorbed to aluminium phosphate 1.45 mg
DTP vaccin Diphtheria, Tetanus an inactivated Poliomyelitis vaccine 1 ml	NVI RVG 17641	Diphtheria-toxoid * ≥ 5 IE Tetanus Toxoid* ≥ 20 IE Inactivated poliovirus type 1 ≥ 20 DE Inactivated poliovirus type 2 ≥ 2 DE Inactivated poliovirus type 3 ≥ 3.5 DE *adsorbed to aluminium phosphate 1. 5 mg
Acellulair kinkhoestvaccin 3 component acellular pertussis vaccine 0.5 ml	GSK RVG 22335	Pertussis toxoid (PT) 25µg Filamenteuze hemagglutinine (FHA) 25µg Pertactin 8µg
BMR vaccin 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.
NeisVac-C 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+}
HBVAXPRO 5microgram 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 aluminiumhydroxyphosphatesulphate 0.25mg *yeast strain Saccharomyces cerevisiae (2150-2-3)

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