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Adverse Events Following Immunisation under the National Vaccination Programme of the Netherlands
Number X - Reports in 2003

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Het rapport in het kort

Gestimuleerde passieve veiligheidsbewaking van het Rijksvaccinatieprogramma; nummer X-Meldingen in 2003

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 meldingen werd 78% als bijwerking van de vaccinaties beschouwd. Het ging hierbij om 1060 ziektebeelden, waarvan 56% heftiger verschijnselen betrof en 44% mildere klachten. Dit aantal bijwerkingen moet in relatie worden gezien tot de 1,5 miljoen vaccinaties en de bijna 7 miljoen vaccincomponenten die daarbij worden toegediend.
Er zijn 1374 meldingen ontvangen in 2003. Het merendeel van de gemelde bijwerkingen betrof de bekende meer gewone klachten, zoals koorts, huilen, bleekheid en lokale verschijnselen. Hangerigheid kan zich op jonge leeftijd op vele manieren uiten. Een klein deel had heftiger verschijnselen zoals zeer hoge koorts, langdurig heftig huilen of forse lokale klachten. Zes kinderen hadden een abces (etterbuil) op de prikplek gekregen. Collaps (wegraking) kwam bij 210 meldingen voor en de zogenoemde verkleurde benen bij 134 kinderen, vooral na de eerste prik. Stuipen, vooral bij de eenjarigen en meestal gepaard met koorts, kwamen bij 70 kinderen voor en werden voor tweederde als bijwerking beschouwd; bij de overige kinderen had de stuip een andere oorzaak. Niet goed te duiden incidenten worden onder “atypische aanvallen” gerubriceerd. In bijna driekwart van deze gevallen was er een mogelijke relatie met de vaccinatie; het gaat dan om episodes met rillerigheid, schrikschokken en gespannenheid of juist een hele slappe houding. Hoewel al deze bijwerkingen omstanders erg kunnen laten schrikken zijn ze medisch gezien niet gevaarlijk en laten ze geen restverschijnselen na. Er zijn geen gevallen van hersenontsteking gemeld in 2003 en evenmin bedreigende allergische reacties. De ernstige infecties die werden gemeld hadden geen relatie met de vaccinaties en datzelfde gold voor de gemelde kinderen met epilepsie of suikerziekte. Het ging hierbij om een toevallige samenloop van gebeurtenissen. Bij de drie gemelde overleden kinderen is het overlijden niet door de vaccinaties veroorzaakt. Een bijzondere en zeldzame mogelijke bijwerking die in 2003 wat vaker dan in andere jaren werd gemeld, was een tijdelijk tekort aan bloedplaatjes (ITP), met name na de vaccinatie tegen bof, mazelen en rodehond (BMR). De reden hiervoor is een studie die het RIVM samen met de kinderartsen hiernaar uitvoert.
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.

Bijwerking, Rijksvaccinatieprogramma, veiligheidsbewaking, vaccinaties, RVP

Abstract

Adverse Events Following Immunisation under the National Vaccination Programme of the Netherlands. Number X - Reports in 2003

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. Reports were received mainly from Child Health Care professionals, primarily by telephone through the operating vaccine information and advisory service. 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 2003 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 1.5 million vaccinations 1374 AEFI were reported Of these, 16 (1.2%) were unclassifiable because of insufficient information. In 78% (1060) of the classifiable events a possible causal relation with vaccination was established and in 22% (298) the events were judged to be chance occurrences. Compared to 2002 there were no relevant changes in numbers, nature, severity or causality of reported adverse events. The Netherlands Vaccination Programme has a very favourable risk balance.

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

Acknowledgements

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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 Hypothyreodism
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 Thrombocytopaenic Purpura
JGZ	Child Health Care
LAREB	Netherlands Pharmacovigilance Foundation
LTR	Laboratory for Vaccine Preventable Diseases (of RIVM)
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
SVM	Foundation for the Advancement of Public Health and Environmental Protection
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). De telefonische informatiedienst van het RIVM is een belangrijk instrument in dit passieve bewakingssysteem. In het RIVM jaarrapport zijn alle meldingen ontvangen in het kalenderjaar opgenomen, ongeacht het oorzakelijk verband met de vaccinatie. Dit rapport over 2003 is het tiende jaarrapport.
Van de spontane meldingen kwam 92% telefonisch binnen. Meldingen kwamen merendeels vanuit de Jeugdgezondheidszorg (82%). Nadere gegevens van anderen dan de melder, bijvoorbeeld van ouders, huisarts of ziekenhuis werden in 82% 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 (88%) telefonisch aan de melder teruggerapporteerd. Schriftelijk verslag, veelal van ernstiger of gecompliceerde ziektebeelden, werd naar alle medisch betrokkenen gestuurd.
In 2003 zijn 1374 meldingen ontvangen, bij 1265 kinderen, op een totaal van meer dan 1,5 miljoen vaccinaties. 16 Meldingen (1,2%) waren niet te beoordelen wegens ontbrekende informatie. 1060 Meldingen (78%) werd als bijwerking beoordeeld met mogelijk, waarschijnlijk of zeker causaal verband met de vaccinaties. Een toevallige samenloop werd aangenomen in 298 (22%) meldingen.
Van de gemelde mildere, zogenaamde “minor” algemene ziekte-, huid- of lokale verschijnselen (663) werd 72% (468) als mogelijke bijwerking geboekt (10 niet te beoordelen). Gemelde zogenoemde “major” postvaccinale gebeurtenissen (711) werden in 84% (592) als mogelijke bijwerking beschouwd (6 niet te beoordelen). Deze “major” verschijnselen betreffen de rubrieken “ziek-major”, stuipen, collaps (flauwtes), verkleurde benen, persistent screaming (aanhoudend krijsen), encefalopathie/-itis (hersenlijden/-ontsteking) en sterfgevallen. Voorts waren er enkele major lokale- en huidverschijnselen. Verkleurde benen (in 1995 voor het eerst afgesplitst van de huidverschijnselen) bij 134 meldingen hadden op zes na een mogelijke causale relatie met de vaccinaties.
Collaps, waaronder atypische en onvolledige episodes, werd 210 maal vastgesteld, in zeven gevallen zonder oorzakelijk verband (1 niet te beoordelen). Daarnaast enkele breath-holding-spells (9), 3 keer zonder oorzakelijk verband, en flauwvallen (25) in oudere kinderen.
Convulsies (70) gingen op zes na gepaard met koorts. 47 Convulsies (68%) werden als mogelijke bijwerking beoordeeld (1 niet te beoordelen). Van de 57 atypische aanvallen hadden er 41 (73%) een mogelijk causaal verband (1 niet te beoordelen). Epilepsie (5) werd in geen van de meldingen als bijwerking beoordeeld, maar als coïncidentie.
Persistent screaming ($\geq$3 uur) werd in alle gevallen (55) als bijwerking beschouwd.
Koorts van $\geq$40,5°C was de werkdiagnose bij 52 kinderen uit de “ziek-major”-groep, op 8 na alle beschouwd als mogelijke bijwerking. Van de 67 andere beelden uit de “ziek major” groep was er 20 keer een mogelijk causaal verband (3 niet te beoordelen). Dit betrof myoclonieën/rillingen (3) en vaccinitis (1) gepaard aan zeer hoge koorts ($\geq$40,5^{o}C). Daarnaast

tekort aan bloedplaatjes (ITP,11), apneu/saturatiedaling (2) en ontregeling van (mogelijke) stofwisselingsziekte (1). Bij de overige 44 meldingen uit de “ziek major”-groep ging het een toevallige samenloop.
Er waren 6 abcessen, met 3 kweken positief voor B-hemolytische streptokokken groep A en 1 kweek na langere tijd positief voor Mycobacterium bovis (BCG-stam). Geen kweken zijn afgenomen bij de overige 2 kinderen met abces. Er waren nog 17 anderszins heftige lokale reacties. Een kind met een “major” huidaandoening bleek uiteindelijk gordelroos te hebben.
In 2003 zijn geen kinderen met encefalopathie /-itis gemeld.
De drie sterfgevallen die in 2003 zijn gemeld, zijn alle na uitgebreide evaluatie als coïncidentele gebeurtenis beoordeeld. Bij twee kinderen heeft de vaccinatie mogelijk wel enige indirecte rol gespeeld. Een kind overleed aan de complicaties van schudletsel, mogelijk door paniek bij de ouder. Bij het andere kind werd te lang aangenomen dat het een bijwerking van de vaccinaties betrof terwijl het in werkelijkheid ging om een meningokokken B-sepsis. Dit illustreert de noodzaak van voorlichting over het gevaar van schudden onder alle omstandigheden en van waakzaamheid van artsen en ouders voor andere oorzaken van postvaccinale verschijnselen.
De meeste meldingen (1019) betroffen gelijktijdige vaccinaties tegen difterie, kinkhoest, tetanus, polio (DKTP) en tegen Haemophilus type B infectie (Hib). Bof, mazelen, rodehond (BMR) vaccin was betrokken in 222 van de meldingen, waarvan 175 maal gecombineerd met andere vaccins. In 59% was er een mogelijke causale relatie met de BMR. Dit was 72% voor de andere vaccin(combinatie)s.
Vergeleken met 2002 was er in 2003 een kleine stijging in het aantal meldingen. Dit is toe te schrijven aan de nieuwe vaccins in het programma, een aantal late meldingen uit de menC-campagne en een aantal opgenomen meldingen vanuit een actieve peiling naar ITP.
Het totaal aantal bijwerkingen moet in relatie gezien worden met het grote aantal verrichte vaccinaties, met meer dan 1,5 miljoen prikken en de bijna 7 miljoen toegediende vaccincomponenten. De grote gezondheidwinst die de vaccinaties van het RVP opleveren, 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). The 24h-telephone service for reporting and consultation is an important tool for this enhanced passive surveillance system. RIVM reports fully, over all incoming reports in a calendar year, irrespective of causal relation, since 1994. This report on 2003 is the tenth annual report.
The majority of reports (92%) came in by telephone. Child Health Clinic staff are the main reporters (82%). Parents, GP's and/or hospital provided additional data on request (82%). 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 (88%). Written assessments, in case of more serious and complicated events, was sent to all medical professionals involved.
In 2003, on a total of over 1.5 million vaccinations, 1374 AEFI were submitted, concerning 1265 children. Of these only 16 (1.2%) were not classifiable because of missing information. Of the classifiable events 1060 (78%) were judged to be possibly, probably or definitely causally related with the vaccination (adverse reactions) and 298 (22%) were considered coincidental events.
So-called "minor" local, skin or systemic events were registered in 663 cases with 468 (72%) classified as possible adverse reactions (10 reports could not be classified).
The so-called "major" adverse events (grouped under convulsions, collapse, discoloured legs, persistent screaming, major-illness and death with inclusion of some skin and local reactions) occurred in 711 cases, in 84% (592) possible adverse reactions (6 reports unclassifiable).
Discoloured legs were reported 134 times with possible causal relation in all but six.
Collapse, including atypical and incomplete episodes, was diagnosed 210 times, in only 7 cases without causal relation (1 unclassifiable). Nine breath holding spells were reported, in 6 with inferred causality and 25 times fainting in older children.
Convulsions were diagnosed in 70 cases, in all but 6 with fever. Of these 47 (68%) were considered causally related (1 unclassifiable). Atypical attack (57) had possible causal relation in 73% (41) of cases (1 unclassifiable). Epilepsy (5) was considered not causally related with the vaccinations in all instances.
All reports of persistent screaming (55) were considered adverse reactions.
Fever of $\geq$40.5°C was the working diagnosis in 52 reports of the major-illness group, in all but 8 with inferred causality. Of the other 67 major-illness cases 20 had a possible causal relation. These events were myoclonics/chills (3) and "vaccinitis" (1) with very high fever ($\geq$40.5^{o}C). Furthermore ITP (11), apnoea/decreased saturation (2) and derangement of possible metabolic disorder (1). The other 44 reported cases were considered to be unrelated (3 unclassifiable). There were 6 abscesses, with 3 cultures positive for Haemolytic Streptococcus group A and 1 culture after a long time positive for Mycobacterium bovis

(BCG-strain). Of the two others no cultures were taken. 17 reported local reactions were considered “major”. One child with “major” skin condition eventually appeared to have herpes zoster.
No cases of encephalopathy /-itis were reported in 2003 and no anaphylactic shock.
In 2003 all three reported deaths were considered chance occurrences after thorough assessment. In two children however the vaccination may have played some indirect role. The one child died from complications of shaken baby injuries, possibly inflicted in panic by the parent. In the other child the illness was attributed to the vaccination for too long with fatal delay and the child died because of meningococcal B-septicaemia. This illustrates the importance of stressing the danger of shaking in all circumstances and of alertness in parents and professionals on other causes of adverse events following vaccinations.
Most frequently (1019) 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 222 times, 175 times with simultaneous other vaccines. In 59% of these reports there was possible causal relation with MMR. For the other vaccine combinations this percentage was 72%.
In 2003 the number of reports was somewhat higher than in 2002. This can be well explained by the new vaccine additions in the programme, some late MenC-campaign reports and extra reports included from an active study on ITP.
The total of 1374 reports should be weighted against the large number of vaccines administered, with over 1.5 million vaccinations and the nearly 7 million vaccine components. The risk balance greatly favours the continuation of the vaccination programme.

1 Introduction

Identification, registration, and assessment of adverse events following drug-use are important aspects of post marketing surveillance. Safety surveillance is even more important in the programmatic use of preventive strategies and intervention, 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 immunisations (AEFI) under the National Vaccination Programme (RVP). Already in 1962, with the introduction of the combined Diphtheria, Tetanus, whole-cell Pertussis and inactivated Polio vaccine (DPTP), a passive surveillance system has been adopted. Since 1984 the safety of the RVP has been evaluated in close collaboration with the Health Council (GR). Following a realignment of the functions of GR and RIVM, GR no longer reassesses individual cases from 2003 onwards. Plans were made for setting up a RIVM expert panel.
Since 1994 following the introduction of a vaccine against Haemophilus influenzae type b (Hib) RIVM has reported annually on reported adverse events following immunisation under the national vaccination programme. 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. This 2003 report contains a description of the procedures for soliciting notifications, verification of symptoms, diagnosis according to case definitions, and causality assessment. It includes a detailed 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 some specific adverse events and their relation to the vaccination. Special attention will be given to underreporting, to prevention of adverse events and contra-indications, to trends or other signals. Notifications are followed with special attention to age and schedule specific adverse events, in view of the accelerated schedule, and new additions to the programme. In 2002 the acellular pertussis vaccine was added for the four-year-olds, and menC introduced at 14 months since September 2002. HepB vaccine was added to the programme for risk group children and mixed administration of DPTP-Hib registered in 2003. The safety surveillance system has been repositioned within RIVM as off January 2002, ensuring independent surveillance from vaccine manufacturers. This process has continued in 2003 with the splitting off of the vaccine department as Netherlands Vaccine Institute (NVI). NVI, and no longer RIVM, is marketing authorisation holder for several former RIVM vaccines used in the programme. The GR reconsidered its role in the safety evaluation of the vaccination programme also in the light of this reorganisation. This tenth RIVM report on adverse events is only issued in English. The summary and aggregated tables will be posted on the RVP web site, www.rvp.nl. A five-year overview in Dutch is in preparation.

2 Post Marketing Surveillance

Post marketing surveillance (PMS) consists of all actions towards better knowledge and understanding of (adverse) effects of vaccines beyond the pre-registration research. This is particularly relevant for the identification of rare as well as late adverse reactions, as their rate of occurrence can only be estimated after vaccine use in large populations over a long time [1]. Insight in overdose consequences or use in special groups or circumstances and interactions can be gained only through PMS. Moreover, actual field effectiveness of many or most vaccines and vaccination programmes can only be determined after use over a long time in unselected populations and circumstances. The surveillance of the RVP is an acknowledged task of the National Institute for Public Health and the Environment (RIVM): the safety surveillance by the Laboratory for Vaccine-Preventable diseases (LTR) for the year under report and the surveillance of effectiveness by the Centre for Infectious Disease Epidemiology (CIE) [2]. Currently the safety surveillance is also positioned within CIE. Requirements for Post Marketing Surveillance of adverse events have been stipulated in Dutch and European guidelines and legislation [3,4]. 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 [5]. The WHO keeps a register of adverse reactions as part of the global drug-monitoring programme [6]. Currently there are several international projects to achieve increased quality of safety surveillance and to establish a register specifically for vaccines and vaccination programmes [7,8,9].

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 [10,11]. Not only true side effects but also events with only temporal association with vaccination may jeopardise uptake of the vaccination programme [12]. 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 [13]. The diphtheria epidemics in Eastern Europe are also result of anxiety about safety of vaccination (procedures) [14]. But also recently concern about safety rather than actual causal associations caused cessation of the hepatitis B programme in France [15,16]. Even at this moment the uptake of MMR in the UK 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 [10,17,18,19,2021,22,23,24,25]. Subsequent (local) measles epidemics have occurred [26,27,28,29].

To counteract similar (unfounded) disquiet in the Netherlands, RIVM has looked for a broader framework of safety surveillance, with a more scientific approach and independent reassessment. This led to the installation of a permanent committee of the Health Council

(GR) in 1984. This committee has reassessed the more severe events presented by RIVM up till 2003. The repositioning of the safety surveillance within RIVM led to reconsideration of this GR role. For the year under report this has led to a change in procedures, both for GR and RIVM. The GR has advised the Minister of Health on the safety of the Vaccination Programme with annual reports, up till 2003 (in preparation) [30,31]. RIVM is setting up a RIVM expert panel for re-evaluation and scientific discussion on individual case (group) level. Since the GR reports had no direct reference to year of notification or vaccination and contain a selection of reported adverse events they cannot be used for analysis of trends or patterns in reporting of events nor for comparison of vaccines, lots or schedules. The annual reports of RIVM on adverse events aim to contribute to these goals, however, and may lead to specific follow up and systematic study of selected adverse events [32,33,34,35,36,37,38,39,40,41]. We hope this will lead to 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. These reports may also serve for the purpose of public accountability for the safety of the programme [42].

3 The Netherlands Vaccination Programme

3.1 Vaccines and Schedule

In the Netherlands mass vaccinations of children were undertaken from 1952 onwards, with institution of the National Vaccination Programme (RVP) in 1957. From the start all vaccinations covered, were free of charge and have never been mandatory. Although a law existed on smallpox vaccinations, this law has never been enforced. With the eradication of smallpox vaccinations were abandoned and this law was revoked in 1978 [43,44]. At first mono-vaccines against diphtheria, pertussis and tetanus were used and the combined DPT vaccine since 1957. After the polio epidemic in 1956, vaccination against poliomyelitis was added. From 1962 onwards the combined DPTP vaccine, with an enhanced polio component (1978), is in use for vaccination of infants and young children and DTP(olio) for revaccination of older children. Rubella vaccination for 11 year old girls was added in 1974 and measles vaccination for 14 months old children in 1976. In 1987 the combined measles, mumps and rubella (MMR) vaccine replaced the mono-vaccines in a two-dose schedule for all children (14 months and 9 years). Mid 1993 vaccination against (invasive) infection with Haemophilus influenzae type b (Hib) was added for children born after April 1st 1993. The actual RVP schedule of 2003 is included in box 1 (appendix 1).
From March 1999 onwards vaccinations start at an earlier age in the programme, at two months of age in stead of three. This was decided in order to achieve protection as early as possible for the youngest, most vulnerable children, because of the resurgence of pertussis in the Netherlands. The aim is to have given all children the third dose at five months of age. It was shown that with the prior schedule about one quart of children had not finished their primary series before six months of age [45]. For the birth cohort of 1998 an extra pertussis booster vaccination has been included with a single acellular pertussis mono-vaccine (aK), administered simultaneously with the fifth DTP at approximately four years of age [46].

Box 1. Schedule of the National Vaccination Programme of the Netherlands in 2003*

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	+	aK		
9 years	DTP6	+	MMR2		

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

From September 2002 onwards MenC vaccine is also included in the programme following a national MenC campaign for all children 1-19 years [47,48]. HepB-vaccination was included for children born to parents originating from countries with moderate and high risk of hepatitis B carriage from 2003 onwards, in addition to the passive and active immunisation of children born to HBsAg positive mothers [49]. For these latter children it meant a change of schedule

from four doses at 2, 3, 4 and 11 months to three doses at 2, 4 and 11 months with change to paediatric formulation. In Amsterdam, with a higher prevalence of HBV carriers, a different schedule and delivery system is still operational. In march 2003 DPTP-Hib was registered for mixed administration in stead of two separate injections. BCG vaccination is not included in the RVP. Vaccination is however offered to children with higher risk of acquiring tuberculosis when travelling to or staying in countries with a high prevalence, free of charge. Usually BCG vaccination takes place in the second half-year of life [43]. Children of refugees and those awaiting political asylum have an accelerated schedule for MMR and are offered catch up doses up till the age of 19 years [43]. For the RVP this age limit is 13 years.
DPTP, DTP and MMR are produced by NVI (Netherlands Vaccine Institute); Hib (PRP-T) vaccine is produced by Aventis-Pasteur-Merieux but registered in special presentation form by NVI. aK is produced and registered by GlaxoSmithKline, with final bulk into vials by NVI. MenC-vaccine is from Baxter. From December 1997 onwards the combined DPTP vaccine contains a better-defined pertussis component with on average a higher potency in the mouse protection test. SerumStatenInstitute produces BCG.
(Summarised product characteristics appendix 2 and full documents: www.cbg-meb.nl)

3.2 Vaccine Distribution and Registration

Vaccines for the RVP are supplied by NVI and are kept in depot at a regional level at the Provincial Immunisation Administration (PEA) [43,50]. 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 Care Service (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.
The PEA sends an invitation for vaccination, with a vaccination-registration document and information, to the parents of every child in the second month of life or after immigration. A bar coded card for every scheduled vaccine dose is included. These cards are to be returned to the PEA by the provider after the vaccine is administered. Duplicate cards are available at the vaccination settings. Returned cards are also used for remuneration of the costs of vaccinating (approximately 5 Euro per vaccine) to the Health Care organisation. All administered vaccinations are entered in the databases of the PEA on individual level; the PEA sends reminders to the child's address if necessary. The databases serve also the providers who can check the vaccination status of individual children, or of the population they serve. The data of the PEA follow the child when it moves from one place to another. Currently a new national web based database is being built with improvements in functionalities.
The PEA databases also contain results of heel prick tests and of prenatal hepatitis B screening and subsequent vaccinations and results of prenatal tests on blood group incompatibilities and irregular antibodies.

3.3 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 [44]. Up till four years of age (Pre School) children attend the Child Health Clinic (CB) regularly. At school entry the Municipal Health Care 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 first contact with the family usually occurs less than a week after birth when a nurse visits the home for the heel prick test on phenylketonuria, congenital hypothyroidism and adrenogenital syndrome (PKU/CHT/AGS with MCADD-in pilot regions). At a special home visit approximately two weeks after birth, parents get information on Child Health and an invitation for the first CB visit at one month of age. The nurse may make additional house calls.Up till 15 months of age about ten CB visits take place during which physical check-ups are performed. These include full medical history and growth and developmental screening at appropriate ages and tests of vision and hearing. Weight, height and head circumferences are recorded on growth charts. Validated test forms are used for developmental follow up. Data on physical examination are also recorded in a standardised form. Parents get advice on food and supplements and information about behaviour, safety issues and upbringing. Interval between visits gets larger as age increases, from four weeks to three months up till the age of 15 months and after that with increasing intervals of three, six and nine months up till the age of four years. The child is seen depending on age specific problems, alternating by a nurse or a physician specially trained in Child Health. On individual basis this schedule may be adjusted, and the nurse may make house calls.

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 aK 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, with a possibility for catch up till the age of 13 years. For refugees and asylum seekers the programme covers vaccination up till 19 years of age.

Attendance of Child Health Clinics is very high, up to 99% and vaccination coverage for DPTP/Hib is over 97% with a slightly lower uptake for MMR of 95% [51,52,53]. (Accurate numbers on birth cohorts 2001 and 2002 have not been released as yet).

3.4 Safety Surveillance

Since 1962 an adverse event (AE) surveillance system for the National Vaccination Programme (RVP) has been in effect. This enhanced passive reporting system includes a (24-hr) telephone service. This service is also available for consultation and advice on vaccination matters like schedules, contra-indications and precautions. This permanent availability and easy accessibility of the surveillance system make the reporting channel both

fast and direct. AE may also be reported by regular mail, fax or e-mail.
The annually distributed vaccination programme (appendix 1) by the Inspectorate of Health Care (IGZ) 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 [43]. RIVM promotes reporting through information, education and publications, and by contributing to refresher courses for Child Health Clinic staff. General Practitioners and Paediatricians are informed at symposia and during their training. Feedback to the reporter of AE and other involved professionals has been an important tool in keeping the reporting rate at high levels.
Severe symptoms irrespective of medical intervention and irrespective of assumed causality are 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 those as well.

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 official reports or consultations regarding adverse events. After receipt of a notification, a physician of RIVM reviews the information. Data are verified and the need for additional information is established. Additional information may be obtained from clinic staff, parents, general practitioners and hospital. Also data from the PEA are collected. Upon verification of symptoms and completion of data a (working) diagnosis is made. Interval with the vaccination and duration of the event is established and causality assessed. The feedback includes a description of verified symptoms, diagnosis and causality assessment by RIVM, and advice on subsequent vaccinations. See for detailed description on procedures chapter 5.
Since 1984 the Health Council (GR) re-evaluates reported AE on the basis of formal detailed written assessments by RIVM. These written assessments include the more serious reported events. Criteria for selection of the cases to be presented to GR have been mutually accepted. The other reports are crosschecked sample wise by GR. Since 1994, for reasons specified in chapter 2, RIVM publishes annual reports on adverse events. Repositioning of the safety surveillance system in RIVM in 2002, the reorganisation of the vaccine department to the separate Netherlands Vaccine Institute in 2003 and the changing role of GR in 2003 did lead to a change in procedures for 2003. For further details see paragraph 5.7.

4 Materials

4.1 Post Vaccination Events

Events following immunisations do not necessarily have causal relation with vaccination and some have temporal association only and are in fact merely coincidental [10,11,50]. 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 6 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 or inoculation: 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: 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) [33,34,54,55].

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. Collapse reaction and persistent screaming, occur less frequently and these maybe due to a special susceptibility in certain children.
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 subcutaneous administration of absorbed vaccines or non-sterile materials. Also too deep administration of BCG leading to abscess. 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.

4.2 Notifications

All incoming information on adverse events following immunisations (AEFI) under RVP, whether 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. The same goes for events from active studies. All notifications are

recorded on an individual level. For notifying and information a (24-hr) telephone service is available. This permanent availability with instant consultation and advice makes this notification channel direct, easily accessible and fast, resulting in high quality of data. Notifications are also received by letter, form or fax or email. For further details see paragraphs 3.3 and 3.4 and chapter 5 on methods.
Notifications can be subdivided in *single, multiple* and *compound* reports (see box 4). Most reports 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 5.5). 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

4.3 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”.

5 Methods

5.1 Analysis

The processing and evaluation of notifications of adverse events is directed by a standard operating procedure (SOP 12 N-GCP-08). A physician reviews every incoming notification. The data are verified and the need for additional information is determined. A (working) diagnosis is made on the basis of the signs and symptoms, with assessment of the severity, duration and time interval. Causality is assessed on the basis of the type of vaccine, time-interval and presumed pathophysiological mechanism of symptoms and alternative or other plausible causes of the event. The reporter is informed on the likelihood of a causal relation between vaccination and event and given advice on subsequent vaccinations. Usually this is covered in the reporting telephone call or in a later feedback call. A formal written assessment is only made of selected severe events or “alarming” less severe events and sent to all involved physicians. Anonymised copies of these written assessments are sent to the medical consultant of the PEA (MAE). These documents constituted the main source materials for reassessment by the committee of the GR and their subsequent annual advice to the Minister of Health. They may also form the core material for discussion in the RIVM expert panel. For further details see the following paragraphs of this chapter. The change in the positioning of the safety surveillance within RIVM and the splitting off of the vaccine department to form NVI with subsequent change in role of GR did affect the procedures in the year under report (2003).

5.2 Additional Information

Necessary data on vaccines, symptoms, circumstances and medical history are usually obtained in the notifying telephone conversation with the reporter, usually Child Health Clinic staff. They (should) have the chart of the child ready for this purpose. In case of incomplete records or severe, complex or difficult to interpret events, the involved GP or hospital is contacted. As is often the case, apprehension, conflicting or missing data, makes it necessary to take a full history from the parents who are asked to provide a detailed description of the adverse event and circumstances. Permission to request information from medical records is obtained also.

5.3 Working Diagnosis

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 (see paragraph 5.5) and for other diagnoses current medical standards are used. In case of doubt, confusing information, or difficulty in interpretation, physicians of RIVM discuss the case in periodic clinical conferences. Minor difficulties in

assessment may lead to ad hoc consultations and discussions to arrive at consensus.

5.4 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 5. 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 (see 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, but 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 6. 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 in case individual risk factors exist. This may have implications for management of side effects or contraindications. See also paragraph 4.1 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.

5.5 Event Categories

After assessment, all adverse events 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. Discoloured legs are a separate category for the purpose of aggregated analysis from 1995 onwards. Formerly these events were either classified under skin symptoms or under local reactions (see also box 7). For classification case definitions are used. Historically adverse events are subdivided in minor and major events. 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. Hospitalisation per se does not preclude uptake in the minor category. 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. Prolonged mild or moderate fever is considered minor illness.
- Persistent screaming: (sudden) screaming, non-consolable and lasting for three hours or more, without one of the other specific diagnostic groups being applicable. This

considered a major event.

- General skin symptoms: skin symptoms that are not 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 and categorised separately since 1995.
- 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 white phase 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.
- Fits: convulsions are all episodes with tonic and/or clonic muscle spasms and loss of consciousness. There is discrimination by body temperature in non-febrile and febrile convulsions. If fever is $\geq$38.5°C it is booked as febrile convulsion unless the convulsion is symptomatic for meningitis or for other illness. Febrile seizures of more than 15 minutes or asymmetrical or recurring within 24 hours are complex as opposed to simple (classic). Definite epileptic fits or epilepsy are included in this category also. Unspecifiable atypical attacks are a separate group under fits. These are paroxysmal occurrences without the specific criteria for collapse or convulsions or could not be diagnosed definitely as chills or myoclonics e.g. Nocturnal myoclonics are not included, neither are episodes of irritability, jitteriness or chills; these are grouped under general illness.
- Encephalitis or encephalopathy: children younger than 24 months with encephalopathy have an explicit or marked loss of consciousness for at least 24 hours which is not caused by intoxication and not explicable as post-ictal state. In children older than 24 months at least 2 of the 3 following criteria must be fulfilled:
  - change in mental status like disorientation, delirium or psychosis not caused by drugs;
  - marked decrease in consciousness not caused by seizures or medication;
  - seizures with (long lasting) loss of consciousness.

  Also signs of increased intra-cranial pressure may be present. In encephalitis, apart from the symptoms of encephalopathy there are additional signs of inflammation as fever and elevated cell counts in the cerebrospinal fluid.
- Anaphylactic shock: circulatory insufficiency with hypotension and life threatening hypoperfusion of vital organs with or without laryngeal oedema or bronchospasm. This reaction should be in close temporal relation with intake of an allergen and with type I

allergic mechanism involved. Urticaria or wheezing alone is not included.

- Death: all reported children who died following immunisation are included in this category and not under one of the other listed categories.

Box 7. 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		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

5.6 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. Severe and otherwise important events are discussed in the periodic clinical conference among the physicians of RIVM, before final assessment, critically reviewing from different angles in order to reach consensus; of this annotation is included in the file. All notifications are, after completion of assessment and feedback, coded on a structured form for future aggregated analyses and annual reports. This coding is entered in the (electronic) logbook in which all incoming adverse events are entered on the date of notification. A single physician does all the coding in order to achieve maximal consistency. This way there is of every notification a time spaced second appraisal. If there are discrepancies, the assessment is discussed with the original appraiser or a colleague. If there is new follow-up information, the case is reassessed and depending on the information, the original categorisation may be adapted. This applied also for the reassessments done the GR committee or new scientific information: they may lead to adjustment (see also paragraph below).
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 filled together with the other information on the case. The current electronic logbook (database) does not allow systematic feedback with assessment and advice. Nor do the

resources permit written feedback to all reporters as yet. In time, computer generated feedback forms may be used, including listed verified symptoms, diagnosis and causality assessment with added advice, for most notifications that now get a full written report. The full written reports will be reserved for selected complicated cases that may also be discussed in the RIVM expert panel. A project has been started for a database application, which technically allows for both feedback and aggregated analysis (see paragraph 5.8).

5.7 Health Council

Since 1984 the Health Council (GR) advises the Minister of Health on the safety of the National Vaccination Programme. A permanent committee has been appointed. Currently this expert group includes specialists on the following (different) fields: paediatrics, child health care, public health, epidemiology, microbiology, neurology, immunology, pharmaco-vigilance, pathology, vaccinology. GR has based their safety advice mainly on the re-evaluation of the formal written assessments by RIVM and other available information on the anonymised cases. Together with data from the international medical literature and the aggregated reports of all notifications assessed by RIVM, the final judgement on the safety of the programme is reached. A physician of RIVM is advisory member of this GR committee. Until 2003 GR made a working visit to RIVM annually, to audit the proper procedures and the completeness of registration and the quality and consistence of assessments (commented upon in the GR annual advise to the Ministry of Health). Summarised reassessments of the GR committee have been published in annual GR reports to the Minister of Health. Included are the AEFI, which are reassessed in the working period of the committee. There has been an inherent, considerable and variable lag time between notification and this reassessment. Because the RIVM annual reports include all reported cases in a calendar year of which selected ones are included in the GR reports under responsibility of the committee, there is inevitable overlap. Thus numbers should not be added up.
Because of the workload and assessment criteria have been agreed upon, only a selection of listed events have been reassessed from 1996 onwards, by the GR, with review of summarised reports of the other events. This change has resulted in less written assessments since 1996. A redefining of the task of this permanent committee has been done, since the safety surveillance as off 2002 is independent from the manufacturers of vaccines. The reallocation of the vaccine department of the RIVM together with SVM as separate vaccine manufacturer (NVI-Netherlands Vaccine Institute), cut loose from RIVM makes the necessity of secondary independent re-assessment by GR less obvious. The broader scientific discussion of particular adverse events within this GR committee would however add to the value of the safety surveillance. RIVM will set up a RIVM expert panel for this purpose.

5.8 Annual Reports and Aggregated Analysis

The coded forms are used as data sheets for the annual reports. For 2003 all reported events have been coded by one of us (PEVdB), after reappraisal of the information. Grouped events were checked for maximum consistency. Samples of final diagnosis, causality and

categorisation have been discussed in the training programme of new investigators. The development of a robust database is behind schedule; therefore the data for this report have been entered in a temporary (logbook) database with limited possibilities. Trend analysis as planned and more in-depth evaluation will have to wait until the new system is installed.

5.9 Quality Assurance

Assessment of adverse events is directed by standard operating procedure (SOP 12N-GCP-08). There have been internal inspections up till 2002 and the GR regular audit over the years 2001/2002. This has been commented upon in the GR report over 2001 and 2003 (in preparation).

5.10 Medical Control Agency and Pharmacovigilance

From November 2002 onwards RIVM sends expedited reports on so called serious adverse events (SAE) to Lareb, thus allowing the Dutch medical control agency (CBG) to fulfil its obligations towards WHO and EMEA. RIVM and Lareb have mutually agreed upon the structure and content of these reports. Lareb sends reports directly received from other reporters on programmatically used vaccines to RIVM. These procedures will be fine-tuned in 2004.

6 Results

6.1 Number of Reports

In 2003 RIVM received 1374 notifications of adverse events, on a total of nearly 1.4 million vaccination dates with nearly 7 million vaccine components (table 1). These 1374 reports involve 1265 children, compared to 1249 and 1251 in 2002 and 2001.
25 Notifications were compound with two (or more) distinct adverse events after one vaccination date; one child had three distinct events reported. Five of these compound reports were also multiple, with six reported events after a different vaccination date.
74 Notifications were multiple with two (or more) events in one child after different vaccination dates. Four of these concerned three different vaccination dates. Multiple and compound reports are listed under the respective event categories. In 1998, 1999, 2000, 2001 and 2002 there were 26, 44, 40, 65 and 58 multiple reports and 9, 8, 13, 9, and 21 compound reports on a total of 1100, 1197, 1142, 1331 and 1332 reported events, respectively. As described in paragraph 4.2, 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. Type of reports of notified AEFI in 2003

notifications	children	adverse events
single	1166[a]	1166
multiple	74[b]	151
compound	20[c]	41
compound and multiple	5[d]	16
total	1265	1374

[a] 29 children had also reports in previous (14) or following (15) years; these are not included
[b] four children with triple reports
[c] one child had a triple compound report, the others had double reports
[d] one child had two compound reports, the others one compound and one single report

From 1994 onwards comparisons of numbers are valid because the criteria for recording have been consistent, criteria for events eligible for full written assessments have changed however. Even without exact counts of former 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 [32,33,34]. In 1998 there was a significant increase in the number of reports judged to be partly due to increased awareness and apprehension, further reduced underreporting but to some true increase in actual adverse reactions as well [35]. In 1999 there was again an increase in number of reports. This was to be expected because the change in schedule from march 1999 onwards resulted in a larger number of vaccinated infants of about one month cohort with for dose 1, 2 and 3 approximately an extra 50,000 DPTP/Hib vaccinations [36]. Any change in the programme may give rise to increased apprehension and awareness, which might in turn lead to an increase in notifications also. In the current year three schedule changes were in effect. MenC

vaccination at 14 months of age, HepB vaccination for children of originating from middle and high endemic countries (first degree) and administration of mixed DPTP-Hib replacing the two simultaneous injections. There appears to be a gradual increase in the birth cohort also up till 2000 from nearly 190,000 in 1996 to over 208,000 in 2000 [53]. Since then there is gradual decrease to a little above 200,000 in 2003 [56]. 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 at on average a younger age with some more young-age specific events reported [38,39]. (See reports on 1998 - 2002, 000001004, 000001005, 000001006, 000001007 and 000001009, respectively (www.rivm.nl). In the current year the number of reports is a little higher (not statistically significant) than in the two previous years but the number of children concerned is stable. The increase in numbers is in the multiple reports group (5.8% versus 4.4% and 4.9% in 2001 and 2002) and also a little in the compound reports group. Details will be given in the paragraphs below and inference in the discussion.

Table 2. Number of reported AEFI per year (with statistically significant step-up 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

[a] before 1994 registration according to year of vaccination and from 1994 onwards to year of notification
[b] up till up till 1993 total numbers are estimates; from 1994 onwards totals are accurate counts

6.2 Reporters, Source of Information and Feedback

The reporter is the first person to notify RIVM about an adverse event (figure 1). As in previous years the vast majority of reports were made by telephone (table 3). 49 Reports came by regular mail, most frequently as regionally used, special report forms and some as (hospital discharge) letter. Also some reports came in by e-mail (31) or fax (28). These latter numbers have increased somewhat over the last few years. Over previous ten years the absolute number of written reports fluctuated between 25 and 51 with in 2002 an increase to 65. Numbers have increased absolutely but relatively the percentage written reports fluctuates between 2.3% to 6.2% from 1994 to 2002 with 7.9% in 2003.

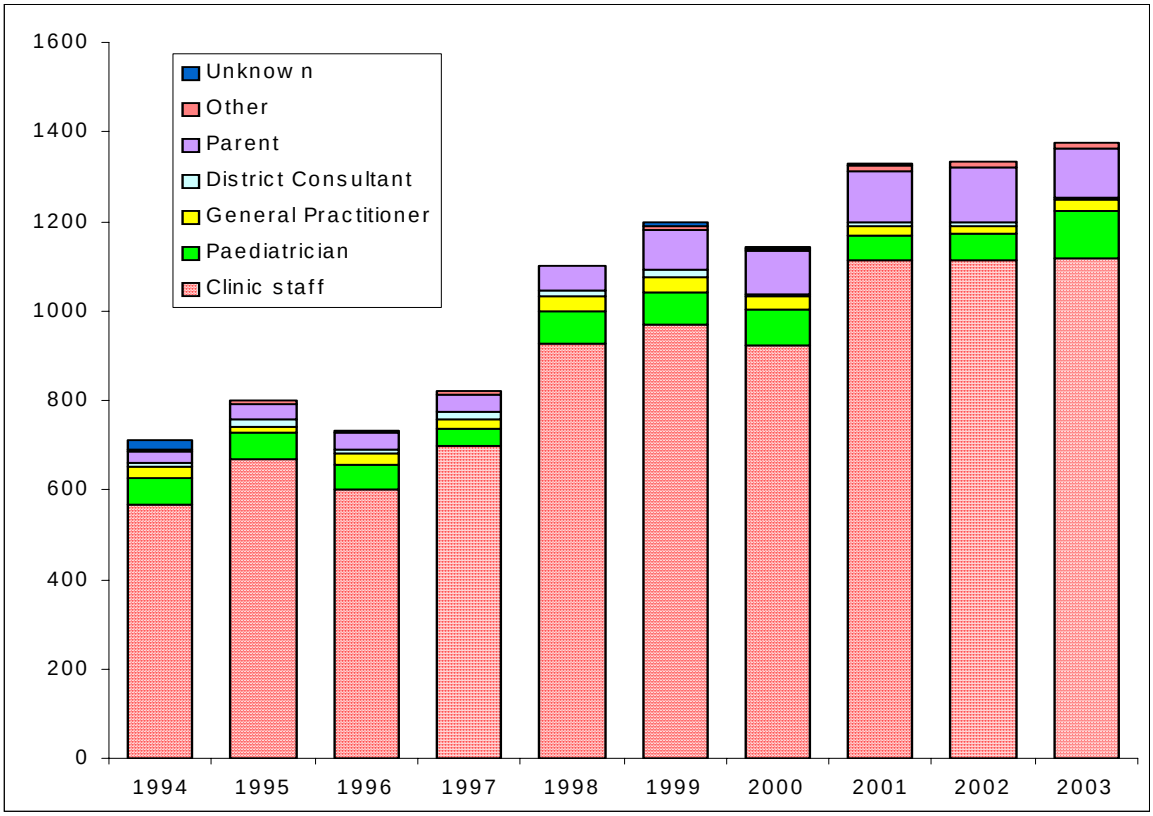


Figure 1. Reporters of adverse events following vaccinations under the RVP

Reports from Child Health Clinics accounted for 1078 (78%), a little lower than in the two previous years (81% in 2001 and 2002, varying between 78% and 84% over the years since 1994). The parents of 113 children (8.2%, also a little lower than in the three previous years with 9.1%, 8.5% and 8.6% in 2002, 2001 and 2000) were the primary reporters; mostly they were advised to do so by clinic staff, but increasingly they "find their own way in". Over the years there has been a slow but steady increase in the percentage of parental reports up till 2000 with absolute numbers increasing up till 2001.

Table 3. Source and reporting route of AEFI in 1994-2003

	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	*tel*	*mail*[c]
Clinic staff[a] Physician	474	548	466	547	678	722	687	794	791	741	*692*	*49*
Nurse	78	102	116	142	219	221	199	290	282	337	*333*	*4*
Paediatrician	60	59	56	39	69	70	80	56	61	108	*74*	*34*
General Practitioner	25	13	26	20	35	34	28	18	17	22	*22*	-
School Health Service	15	18	17	10	31	27	37	31	39	39	*27*	*12*
District Consultant	9	18	11	16	15	16	5	11	8	5	*5*	-
Parent	25	34	35	40	52	91	97	115	121	113	*110*	*3*
Other[b]	5	6	2	7	1	9	7	14	13	9	*3*	*6*
Unknown	21	2	3	1	-	7	2	2	-	-	-	-
Total	712	800	732	822	1100	1197	1142	1331	1332	1374	*1266*	*108*
(% written of total)	(4.9)	(3.4)	(3.4)	(6.2)	(2.3)	(3.8)	(3.3)	(3.8)	(4.9)	(7.9)		

[a] including staff of refugee clinics (3)
[b] including reports by Lareb (5), NMS (1), prosecutor (1), antroposophe (1)
[c] including e-mail (31) and fax (28) reports

The other report sources were more or less stable apart from the paediatricians with an increase in numbers but not so much in relative share of 7.9% of the total number of reports.

(range 4.2%-8.4% from 1994-2002). Some e-mail reports have been included from an active study on ITP from the Netherlands Paediatric Surveillance Unit (NSCK).
In 2003 in 18% of the reported events the reporter was the sole informer and information was received from others also in 82%, both spontaneously and requested, higher than in 2002 (72% in 2002 and in 2001, 78%). In 92% of the reports the clinics (child health care, school health and refugee clinics) supplied information, equal to 2002. Parents were contacted in 83% (1141) of cases (including the reports in which the parents were the sole reporter), sometimes during the notifying telephone call at the Child Health Clinic. This percentage is a higher than in 2002 (76%) and there appears to be a gradual increase in numbers over the years (in 2001 80% and in 2000, 1999 and 1998, 66%, 63% and 62%). Parents were the sole informers in 49 cases (21, 40, 41, 52 and 55 in 1998, 1999, 2000, 2001 and 2002). Hospital specialists supplied information in 24% of the reports (16% in 2002 and 2001, and 18%, 19% and 15% in 2000, 1999 and 1998). See for details table 4.

Table 4. Information sources and events of reported AEFI in 2003

info ⇒	clinic*	+	+	+	+	+	+	+	+	-	-	-	-	-	-	1270 (92.4%)
	parent	-	+	+	+	+	-	-	-	+	+	+	-	-	-	1141 (83.0%)
	gen. pract.	-	-	-	+	+	-	+	+	+	-	-	+	-	-	37 (2.7%)
	hospital	-	-	+	-	+	+	-	+	-	+	-	-	+	-	327 (23.8%)
	other	-	-	-	-	-	-	-	-	-	-	-	-	-	+	5 (0.4%)
event ⇓																
local reaction		28	76	5	2	1	-	-	-	2	2	7	-	-	-	123
general illness	minor	72	301	36	8	1	5	1	-	1	5	24	1	2	3	460
	major	7	46	25	-	-	10	1	2	-	8	-	-	19	1	119
persistent screaming		6	45	2	1	-	-	1	-	-	-	-	-	-	-	55
skin symptoms		19	55	14	3	-	2	2	-	-	-	6	1	1	1	104
discoloured legs		9	104	15	3	-	-	-	-	-	-	3	-	-	-	134
faints		22	140	72	-	2	-	-	1	-	1	5	-	1	-	244
fits		5	48	59	1	1	8	-	-	-	5	4	-	1	-	132
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
encephalopathy/-itis		-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
death		-	-	1	-	1	1	-	-	-	-	-	-	-	-	3
total		168	815	229	18	6	26	5	3	3	21	49	2	24	5	1374

* child health, school health and refugee clinic

Feedback of diagnosis and causality assessment with advice about further vaccinations is a major characteristic of the surveillance system. In about one third of the reports this is (preliminarily) achieved in the notifying phone call. In about another 10-15 percent final assessment did not change the preliminary evaluation substantially. In over half of the reports however cases could only be assessed after further verification and additional information. In about one fifth the additional information supported the initial information fully. In over one third of notifications the original information lacked essential data. In about one third of the reports the notified diagnosis and/or involved vaccines or time intervals needed adjustment. The feedback, for these reports also, is increasingly done by telephone due to a change in procedures (in 1996) and lack of a robust database system and of manpower. See table 2 in paragraph 6.1 for numbers. The intent is however to supply a comprehensive written

feedback with assessment routinely. In 2003 12% of reports got a full written assessment, higher than in the six previous years (6-9%); these were the more complex events or those causing (public) anxiety or uncertainty about subsequent vaccinations (Table 5).

Table 5. Feedback method and events of reported AEFI in 1998-2003

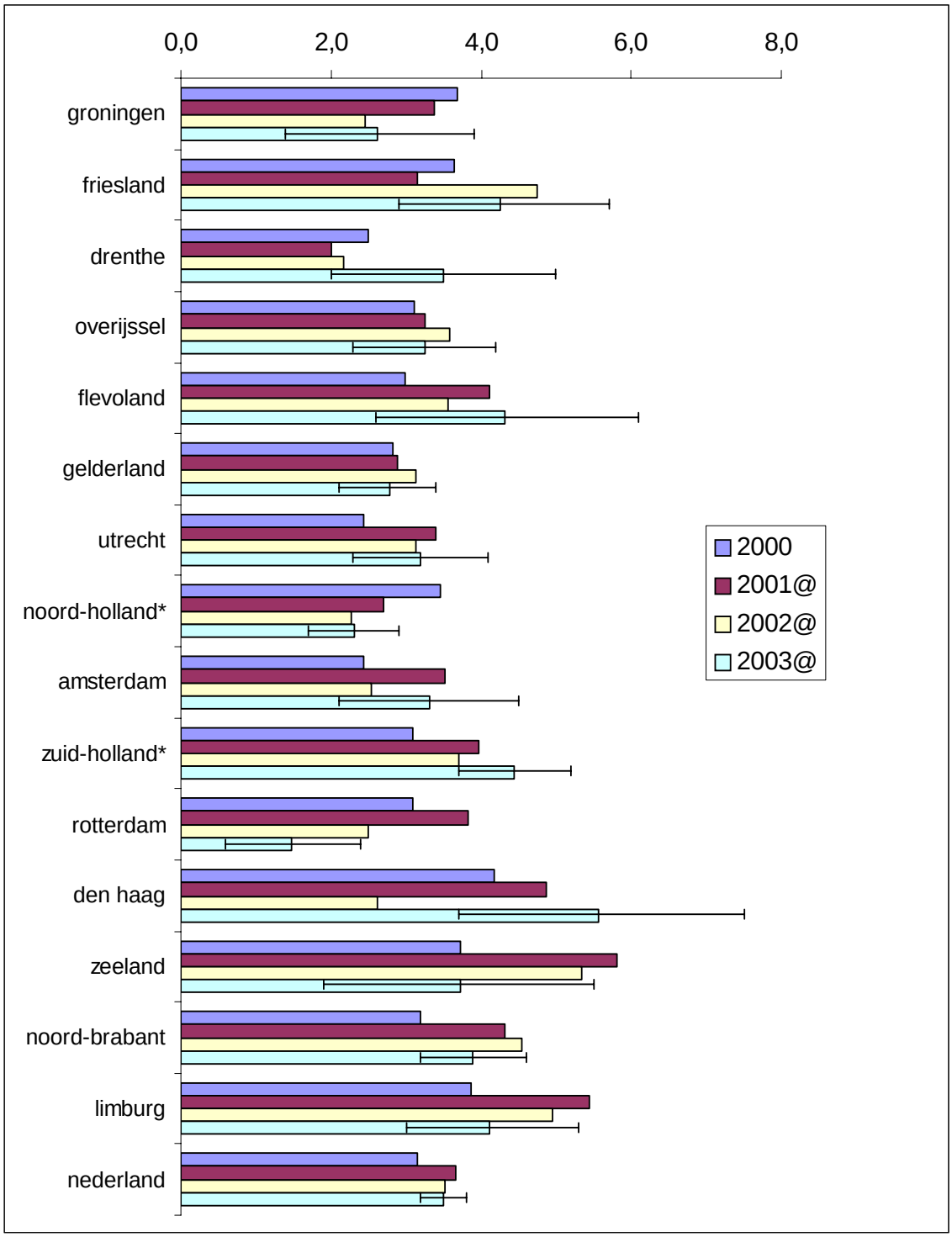
event ⇓ feedback method⇒	mail	tel	2000 total	mail	tel	2001 total	mail	tel	2002 total	mail	tel	2003 total
local reaction	3	72	75	1	89	90	1	119	120	4	119	123
general illness minor	8	358	366	21	426	447	12	405	417	16	444	460
major	18	88	106	14	60	74	20	92	112	51	68	119
persistent screaming	-	39	39	2	47	49	1	45	46	2	53	55
skin symptoms	-	75	75	0	73	73	-	104	104	5	99	104
discoloured legs	5	121	126	14	161	175	4	133	137	9	125	134
faints	17	222	239	34	259	293	20	277	297	35	209	244
fits	15	97	112	22	99	121	16	75	91	47	85	132
anaphylactic shock	-	-	-	-	-	-	-	-	-			
encephalopathy/-itis	1	-	1	2	-	2	-	-	-			
death	3	-	3	7	-	7	8	-	8	3	0	3
total	70	1072	1142	116	1215	1331	82	1250	1332	172	1202	1374

6.3 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 the data from the PEA. In table 6 the rates for 2000, 2001 and 2002 were calculated with vaccination coverage data for the 2000 cohort since later data have not yet been made available [51,52,53]. Like before we use the coverage data for the first three DPTP doses. For 1999 the rates were adjusted for the larger number of vaccinated infants because of the accelerated schedule for the first three doses, since March 1999. Since the regular summarised reports of coverage data do not contain information on timing of the vaccination there will remain inevitable inaccuracies in estimated rates per region for this year [36].

The birth cohort increased from a little below 190,000 in 1996 to 208,521 in 2000 according to the vaccination registers with for 2001 204,741(according to CBS a further decrease in 2002 and 2003, CBS site per November 2004, from 203,149 to 200,297) [56,57]. Comparing the different regions does not show relevant differences in rates according to standardisation with coverage data on birth cohort 2000, between 2001, 2002 and 2003. Reporting rates for only the so-called major events do not show substantial differences between 2001, 2002 and 2003 either. In 2001 there was a substantial increase in both rates compared to 2000 [39]. See table 6 and figure 1. We will present and compare differences in numbers of specific events in the respective paragraphs under 6.8. For 2003 there was a little less dispersion of the reporting rates over the different regions (range 4.1-9.7 compared to 3.0-9.6 in 2002 and 3.7-8.9 in 2001). The 95% confidence intervals for the rates in the different regions contained the country's overall reporting rate in al but four regions however, and in three regions the reporting rate was (statistically significantly) higher than the year before. For the major

events only, only two (small) regions had a reporting rate significantly higher than in 2002. The country average reporting rate for major events is equal in 2002 and 2003 (3.5/1000)



@ for 2000, 2001 and 2002 the coverage data of cohort 1999 have been used since coverage data for the cohorts 2000, 2001 and 2002 have not yet been made available.

* provinces without big cities Amsterdam, Rotterdam, Den Haag

Figure 2. Number of reported AEFI in 1994 till 2003 per 1000 vaccinated infants (with 95% confidence interval bars, proportional, normal approximation)

Table 6. Regional distribution of reported AEFI in 1994-2003, per 1000 vaccinated infants[a] with proportionate confidence intervals (major adverse events)

	1998	2000 (major)	95% c.i 2000 (major)	2001 (major)	95% c.i 2001 (major)	2002 (major)	95% c.i 2002 (major)	2003 (major)	95% c.i 2003 (major)
Groningen	5.3	5.5 (3.7)	3.7-7.3 (2.2-5.2)	4.5 (3.4)	2.8-6.1 (2.0-4.8)	4.0 (2.5)	2.5-5.5 (1.3-3.7)	5,1 (2.6)	3.4-6.8 (1.4-3.9)
Friesland	5.1	5.5 (3.6)	3.9-7.1 (2.3-5.0)	6.4 (3.2)	4.7-8.2 (2.0-4.4)	7.4 (4.7)	5.6-9.3 (3.3-6.2)	7,2 (4.3)	5.3-9.0 (2.9-5.7)
Drenthe	5.8	4.7 (2.5)	3.0-6.4 (1.2-3.8)	3.7 (2.0)	2.1-5.2 (0.9-3.1)	3.0 (2.2)	1.6-4.4 (1.0-3.4)	6,0 (3.5)	4.1-8.0 (2.0-5.0)
Overijssel	4.6	6.3 (3.1)	5.0-7.6 (2.2-4.0)	6.0 (3.3)	4.7-7.2 (2.3-4.2)	6.3 (3.6)	5.0-7.6 (2.6-4.6)	7,3 (3.3)	5.9-8.7 (2.3-4.2)
Flevoland	3.9	4.7 (3.0)	2.9-6.5 (1.5-4.5)	6.9 (4.1)	4.7-9.2 (2.4-5.8)	7.1 (3.6)	4.9-9.4 (2.0-5.2)	7,5 (4.3)	5.2-9.8 (2.6-6.1)
Gelderland	5.2	4.8 (2.8)	3.9-5.6 (2.2-3.5)	5.0 (2.9)	4.2-5.9 (2.2-3.6)	5.7 (3.1)	4.8-6.7 (2.4-3.8)	5,9 (2.8)	5.0-6.9 (2.1-3.4)
Utrecht	6.7	4.9 (2.4)	3.8-6.0 (1.7-3.2)	6.7 (3.4)	5.3-8.0 (2.5-4.3)	6.7 (3.1)	5.4-8.0 (2.3-4.0)	6,8 (3.2)	5.5-8.1 (2.3-4.1)
Noord-Holland[c]	4.7	5.5 (3.5)	4.6-6.5 (2.7-4.2)	5.0 (2.7)	4.1-6.0 (2.0-3.4)	4.1 (2.3)	3.3-4.9 (1.7-2.9)	4.7 (2.3)	3.8-5.5 (1.7-2.9)
Amsterdam	7.2	5.1 (2.4)	3.6-6.5 (1.4-3.4)	7.8 (3.5)	6.0-9.6 (2.3-4.8)	5.8 (2.5)	4.3-7.4 (1.5-3.6)	6,1 (3.3)	4.5-7.7 (2.1-4.5)
Zuid-Holland[c]	6.1	5.6 (3.1)	4.8-6.5 (2.5-3.7)	7.5 (4.0)	6.6-8.5 (3.3-4.7)	7.4 (3.7)	6.4-8.4 (3.0-4.4)	8.3 (4.4)	7.2-9.3 (3.7-5.2)
Rotterdam	3.8	5.3 (3.1)	3.6-7.0 (1.8-4.4)	5.4 (3.8)	3.7-7.2 (2.4-5.3)	5.7 (2.5)	3.9-7.5 (1.3-3.7)	4,1 (1.5)	2.6-5.6 (0.6-2.4)
Den Haag	10.8	6.8 (4.2)	4.7-8.9 (2.5-5.9)	8.9 (4.9)	6.5-11.3(3.1-6.7)	6.4 (2.6)	4.4-8.5 (1.3-3.9)	9,7 (5.6)	7.2-12.3(3.7-7.5)
Zeeland	4.0	5.6 (3.7)	3.6-7.8 (1.9-5.5)	7.7 (5.8)	5.1-10.2(3.5-8.1)	6.7 (5.3)	4.3-9.2 (3.2-7.5)	7.9 (3.7)	5.3-10.5(1.9-5.5)
Noord-Brabant	5.3	6.4 (3.2)	5.5-7.3 (2.7-3.8)	7.7 (4.3)	6.7-8.7 (3.6-5.1)	8.1 (4.6)	7.1-9.1 (3.8-5.3)	7,2 (3.9)	6.3-8.2 (3.2-4.6)
Limburg	6.2	6.2 (3.9)	4.8-7.6 (2.8-5.0)	8.5 (5.4)	6.9-10.1(4.1-6.7)	9.6 (4.9)	7.9-11.4(3.7-6.2)	7,7 (4.1)	6.1-9.2 (3.0-5.3)
Netherlands	5.6	5.6 (3.1)	5.3-6.0 (2.9-3.4)	6.6 (3.7)	6.2-6.9 (3.4-3.9)	6.6 (3.5)	6.2-6.9 (3.3-3.8)	6.8 (3.5)	6.4-7.1 (3.2-3.8)

[a] up till 2000 accurate coverage data are used as published by the Inspectorate of Health Care. Data for 2000-2002 have been adjusted accordingly. For 2000, 2001, 2002 and 2003 coverage data for 2000 have been used.
[b] for 1999 figures are adjusted with approximation of higher number of vaccinated infants because of change in schedule.
[c] provinces without the three big cities (Amsterdam, Rotterdam, Den Haag)
[d] the Netherlands have a birth cohort of approximately 200.000 per year and vaccination coverage of 97% on average for the first three dptp/hib vaccinations.

6.4 Vaccines

In 2003 most notifications were about recent vaccinations (all except 33). These latter notifications arose from concerns about planned booster vaccination or vaccination of younger siblings; in 33% of these cases the parents reported. The vaccine involved in these late reports was often MMR (11). All reports are included in the tables.
In table 7 scheduled vaccines and actually administered vaccines are listed. As in prior years, reports on the first DPTP/Hib dose were the most prevalent (462 compared to 503 in 2002), with lower numbers on subsequent vaccinations and older age, respectively 229 (212), 147 (150), 193 (161) for second, third and fourth dose. See for relative frequencies of involved vaccine doses figure 3. For simultaneous DPTP+Hib vaccinations numbers were 311 and another 708 for mixed DPTP-Hib. This totals to 1019 for combinations of DPTP and Hib a little higher than in 2002 (999) and a little lower than in 2001 (1034), but not significantly different. The number remains significantly higher than the totals of 2000. In 18 reports DPTP was given singly (22, 20, 16, 28 and 20 in 1998, 1999, 2000, 2001 and 2002), without Hib, once with menC and once with MMR however.
50 Children received HepB vaccine simultaneously with their mixed DPTP-Hib as part of the programme for children with a parent originating from moderate and high-risk regions in the world for hepatitis B carriage. One child had a single HepB vaccination as part of the programme.

Table 7. Schedule and vaccines of reported AEFI in 2003

vaccine given⇒ / scheduled ⇓	dptp	dptp hib apart	dptp hib mix	dptp hib mix hepb	hib	hepb	dptp hib mix mmr	mmr	mmr menc	dtp	dtp ak	dtp mmr	menc	bcg	other	2003	2002	2001	2000	1999	1998
dptp1+hib1	5	147	271	38	1	-	-	-	-	-	-	-	-	-	-	462	503	515	418	394	372
dptp2+hib2	4	57[c]	167	1	-	-	-	-	-	-	-	-	-	(1)	-	229	212	229	191	227	205
dptp3+hib3	1	39	95[a]	11	-	1	-	-	-	-	-	-	(1[a])	-	-	147	150	163	133	166	148
dptp4+hib4	3[o]	67[n]	116[p]	-	1[h]	-	3[i]	-	-	3[k]	-	-	(2[i])	-	-	193	161	172	166	188	148
dose?	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	3	5	3	6	8	14
mmr0	-	-	-	-	-	(1[f])	-	7[f]	1	-	-	-	-	(1[f])	(1[f])	8	-	4	4	-	-
mmr1*	-	-	-	-	-	-	-	40	133[d]	-	-	-	-	-	(1[d])	173	150	139	141	139	139
dtp5+ak	4[b]	-	4	-	-	-	1[j]	(1[b])	-	2	67[c]	-	(2[bj])	(1)	-	78	67	41	33	35	34
dtp6+mmr2	-	-	-	-	(1[e])	-	-	1	-	1[e]	-	35[q]	-	-	(1[q])	37	35	47	49	33	33
menc	-	-	-	-	-	-	-	-	-	-	-	-	34[m]	-	-	34	38	-	-	-	-
other	-	-	-	-	-	3	-	-	-	-	-	-	-	3	4[g]	10	11	18	1	7	7
total	18	311	654	50	2(3)	4(5)	4	48(49)	134	6	67	35	34(39)	3(6)	4(7)	1374	1332	1331	1142	1197	1100

[a] once with menC
[b] once with menC and once with mmr
[c] once with bcg
[d] once with prevenar
[e] once with hib
[f] once mmr0 with hepB, yellow fever and bcg
[g] twice pneumo23, once hepA with yellow fever and once rabies vaccine with rabies-immunoglobuline
[h] hib2 in late starter
[i] once mmr0 and twice also menC
[j] once also menC
[k] alternative schedule by parental choice
[m] once before the age of one year
[n] once second catch up dose
[o] once second catch up dose and once third catch up dose
[p] twice first catch up dose and twice second catch up dose
[q] once menACWY

For other vaccines or combinations some numbers differ from those of previous years. There were more reports on the first MMR dose (187 compared to 156 and 157 in 2002 and 2001) of which 132 were scheduled vaccinations with simultaneous MenC, the new addition to the programme from September 2002 onwards. 40 Times MMR1 was given singly and three times simultaneously with DPTP with or without Hib.
Numbers of reports concerning the DTP dose at 4-years of age increased somewhat further. 67 Reports concerned the scheduled combination of DTP and acellular pertussis vaccine (aK). Another 9 reported children received DPTP vaccine with the whole cell pertussis component vaccine of which 5 were mixed DPTP-Hib. These were all catch up doses.
Two children received a single Hib vaccination, by parental choice. Three children received DTP(olio) instead of the scheduled DPTP by parental choice or fear because of prior adverse events (in siblings). The number of reports of events following DTP6/MMR2, always low, was similar to 2002. Late reports of menC in the campaign (30) are included in this report. Two children received separate menC vaccinations under the programme, and one child had menC before the age of one year by parental choice. One report concerned unconjugated MenACWY vaccine given in 2000. The reported adverse events of the menC campaign have been published separately [41]. 10 Children were reported with adverse events following other non-RVP vaccines only. See for further details table 7 and 8 and figure 3.

Table 8. Number of reported AEFI and vaccines in 2003

vaccine	# of reports 2003 (2002)	
DPTP	1037 (1021)	Reported adverse events followed DPTP 1037 times in total, mainly with Hib vaccine (1019); 311 were still the simultaneous DPTP and Hib vaccinations. 708 Reports concerned the mixed DPTP-Hib vaccine, 50 times with simultaneous HepB and one each with simultaneous, MMR or BCG vaccine; three children received the DPTP-Hib vaccine simultaneously with MMR and MenC vaccine. 16 Reports concerned single DPTP vaccine and two DPTP with either MMR or MenC simultaneously.
Hib	1029 (1031)	In total 1029 reported adverse events concerned Hib vaccine. In 311 cases Hib was given with simultaneous DPTP. 708 Reports concerned the mixed DPTP-Hib vaccine, 50 times with simultaneous HepB and one each with simultaneous, MMR or BCG vaccine; three children received the DPTP-Hib vaccine simultaneously with MMR and MenC vaccine. Two children received single Hib vaccine and one DTP and Hib simulteaneously.
MMR	222 (188)	222 Reported adverse events followed MMR. 47 of these were single MMR vaccinations, once at school age and six times before the age of one year. 137 times MMR was administered simultaneously with MenC (once before the age of one year), of which three times also with mixed DPTP-Hib (once before the age of one year) and once with Prevenar. Two children received MMR with simultaneous DPTP or DPTP-Hib. One infant was vaccinated with MMR, HepB, Yellow fever and BCG, prior to travelling. 35 Reported school-aged children received the regular DTP and MMR boosters simultaneously.
MenC	173 (55)	34 children were reported with adverse events after single MenC vaccination, 30 of which were administered as part of the menC campaign in 2002, one was polysaccharide vaccine (menACWY) and three received conjugated MenC vaccine out of schedule by parental choice. 137 times MMR was administered simultaneously with MenC (once before the age of one year), of which three times also with mixed DPTP-Hib (once before the age of one year) and once with Prevenar. One child received MenC with DPTP and one with DPTP-Hib.
DTP	108 (99)	108 reported adverse events followed DTP of which five were single administrations. In the other 103 cases DTP was given with other vaccines at the same time (67 with aK of which one also with BCG, 35 with MMR and once with Hib)
aK	67 (56)	67 Reported adverse events followed administration of acellular pertussis vaccine, in all instances with simultaneous DTP, in one case also with BCG.
HepB	55 (3)	55 adverse event followed HepB vaccine, 50 times with mixed DPTP-Hib simultaneously. Once HepB was given singly and once MMR0, Yellow fever and BCG were given at the same time. Three reported older children received HepB vaccine out of schedule for personal risk factors.
Other	10 (11)	Ten events followed only other than programme vaccines. These included the above mentioned three older children with hepB and another three children with BCG only (apart from two BCG recipients with simultaneous programme vaccines). Two children only got unconjugated Pneumo23, one received HepA and Yellow fever and another Rabies vaccine with anti-rabies immunoglobulins. One infant received apart from scheduled MMR0 and HepB also Yellow fever and BCG vaccine and another child Prevenar at the same time as MenC and MMR1. One reported child received unconjugated menACWY vaccine, prior to the menC campaign.

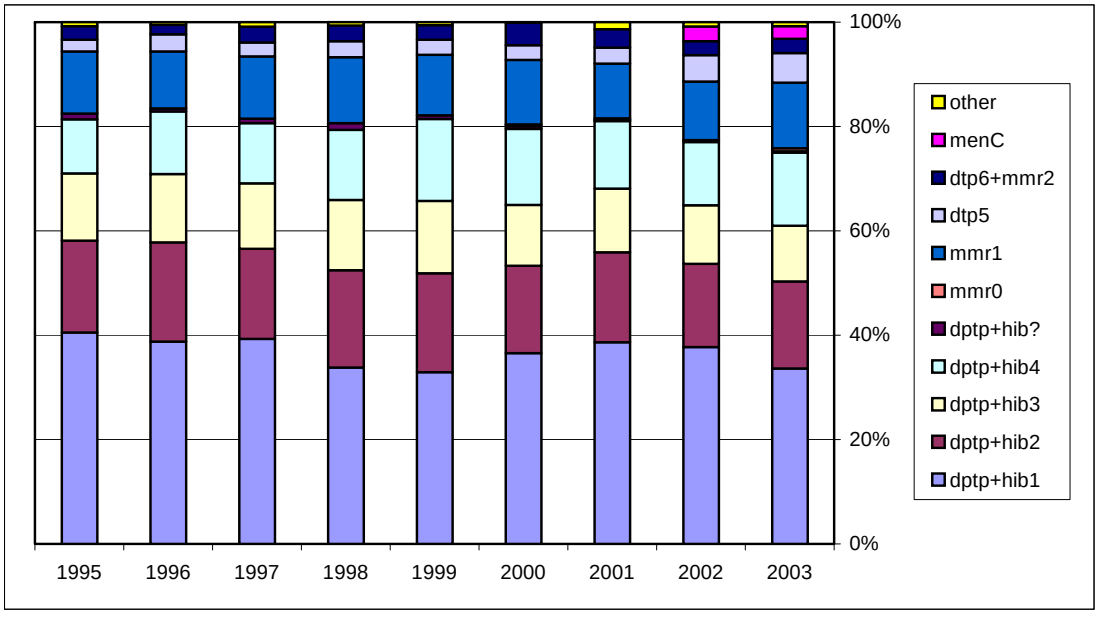


Figure 3. Relative frequencies of vaccine doses in reported AEFI in 1994-2003

Event categories are not equally distributed over the (scheduled) vaccinations (table 9). Faints, mainly collapse, and discoloured legs are most often reported after the first vaccinations, as is persistent screaming. This is consistent over the years.

Table 9. Event category and (scheduled) vaccine dose of reported AEFI in 2003

event ⇓ vaccine⇒*	dptp/ hib1	dptp/ hib2	dptp/ hib3	dptp/ hib4	dptp/ hib?	mmr 0	mmr 1	dtp 5	dtp6/ mmr2	menC	other	total 2003	2002	2001	2000	1999	1998
local reaction	26	13	13	24	1	-	1	28	15	1	1	123	120	90	75	89	69
general illness minor	153	73	51	66	2	4	74	11	8	14	4	460	417	447	366	373	405
major	16	16	8	28	-	2	26	8	3	10	2	119	112	74	106	111	85
persistent screaming	32	14	7	2	-	-	-	-	-	-	-	55	46	49	39	34	29
skin symptoms	22	15	16	13	-	2	17	8	6	4	1	104	104	73	75	85	75
discoloured legs	53	48	20	7	-	-	2	4	-	-	-	134	137	175	126	130	125
faints	153	37	20	8	-	-	2	17	3	2	2	244	297	293	239	244	174
fits	7	12	12	45	-	-	49	2	2	3	-	132	91	121	112	123	133
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-		-	-	-	-	-
encephalopathy/-itis	-	-	-	-	-	-	-	-	-	-	-	-	-	2	1	1	-
death	-	1	-	-	-	-	2	-	-	-	-	3	8	7	3	7	5
total	462	229	147	193	3	8	173	78	37	34	10	1374	1332	1331	1142	1197	1100

* scheduled vaccines are listed. See for more precise description table 5 and the respective event categories

Convulsions, especially febrile, are reported more frequently after the fourth DPTP/Hib and the first MMR, than at younger ages. No children with anaphylactic shock were reported and no cases of encephalopathy/encephalitis. Three 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.

Compared to 2002 the total number has gone up somewhat. Within and between the different event categories there are some changes. These will be commented upon also in the specific event paragraphs. Absolute numbers may be deceptive as the rate depends on actual number of vaccinations. The vaccine coverage data are not yet available for this reporting period.

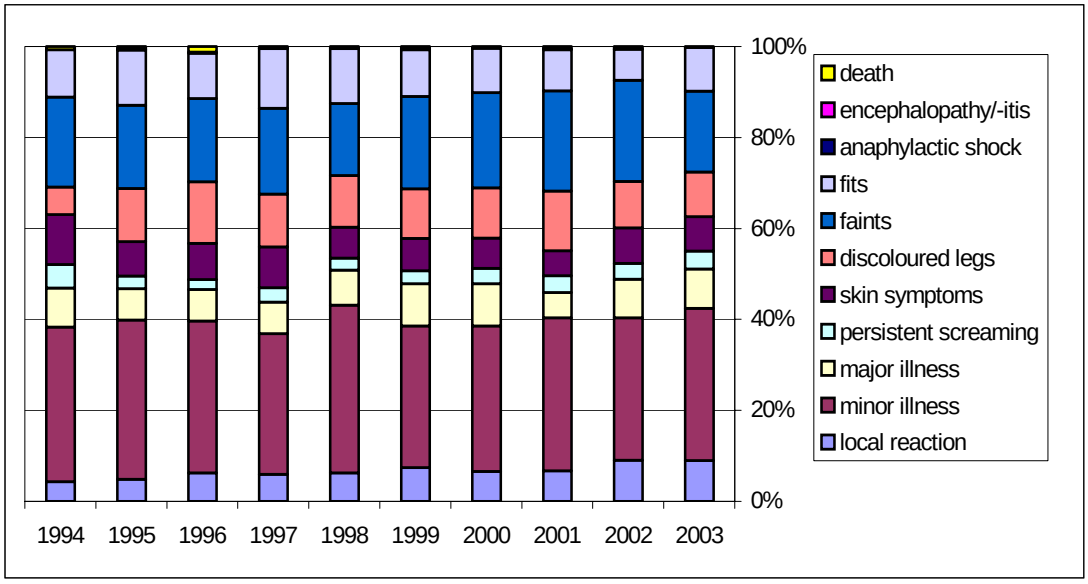


Figure 4. Relative frequencies of events in reported AEFI 1994-2003

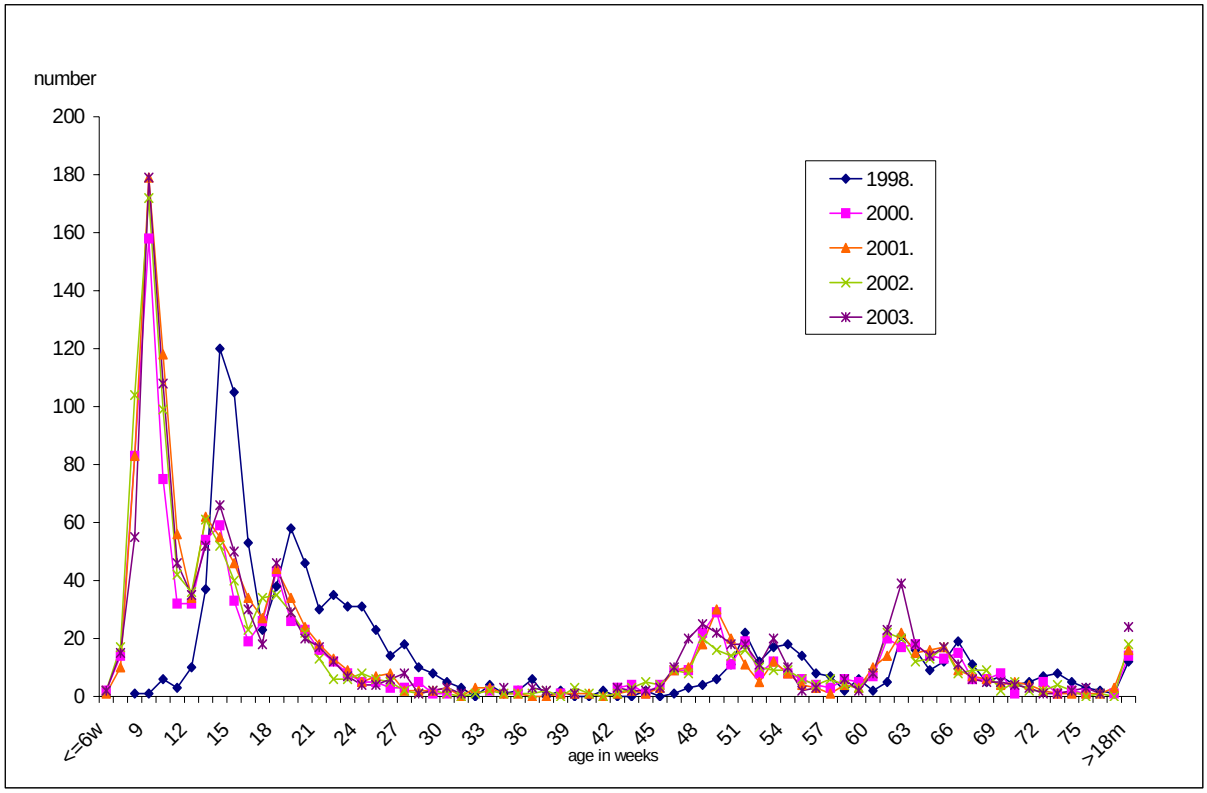


Figure 5. Age distribution of reported AEFI in 1998, 2000, 2001, 2002 and 2003

The relative frequency of the different event categories is more or less the same over the years (figure 4). General illness is the largest category over the years, with a relative frequency of around 40%.
The age distribution is again given in figure 5, comparing 1998 under the old schedule and 2000-2003, reflecting the new schedule in the age of the reported children. 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.

6.5 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 5.5. The share of the so-called major events in total (711 of 1374, 52%, with positive causality 43%) was a little lower than in 2002 (54%and 47%) and 2001 (56% and 49%), figure 6. See also for causality under paragraph 6.7.
The level of medical intervention may also illustrate the impact of adverse events. In 19% (266) of reported events no medical help was sought or was not reported or recorded by us and nearly 15% of the parents (201) administered paracetamol suppositories, diazepam by rectiole or some skin ointment for instance (in 2002, 21% and 14%, in 2001, 20% and 13% and in 2000, 22% and 12%, respectively). 66% Of the parents contacted the clinic or GP, called the ambulance or went to hospital, with 13 % admittance. In 1997, 1998, 1999, 2000, 2001 and 2002 these latter percentages were 52%, 60%, 64%, 66%, 63% and 60% with 11%, 10 %, 12%, 13%, 11% and 10% for admittance respectively. Table 10 and figure 7 show intervention according to highest level used.

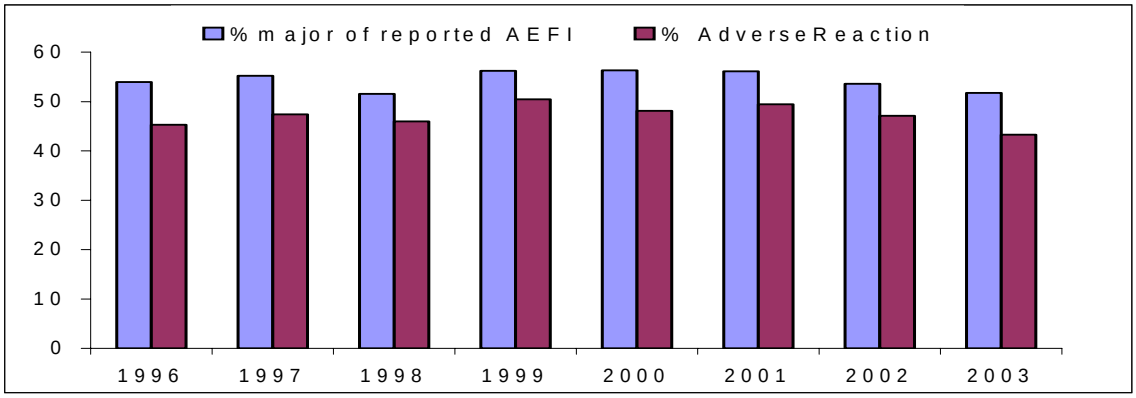


Figure 6. Share of reported major AEFI and of major Adverse Reactions in 1996-2003

Table 10. Medical intervention and events of reported AEFI in 2003

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	10	19	17	31	7	26	-	3	1	5	4	-	123
general illness minor	54	59	87	35	41	108	-	30	12	15	19	-	460
major	5	3	11	-	10	26	-	19	1	43	1	-	119
persistent screaming	8	4	27	3	4	7	-	-	-	1	1	-	55
skin symptoms	10	11	3	12	3	41	-	14	2	3	5	-	104
discoloured legs	8	19	31	4	12	41	2	3	5	6	3	-	134
faints	13	30	22	25	15	56	5	8	18	52	-	-	244
fits	9	4	3	-	14	24	6	8	14	49	1	-	132
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	-	-	-	-	-	-	-	-	-	-
death	-	-	-	-	-	-	-	-	-	1	-	2	3
total 2003	117	149	201	110	106	329	13	85	53	175	34	2	1374

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

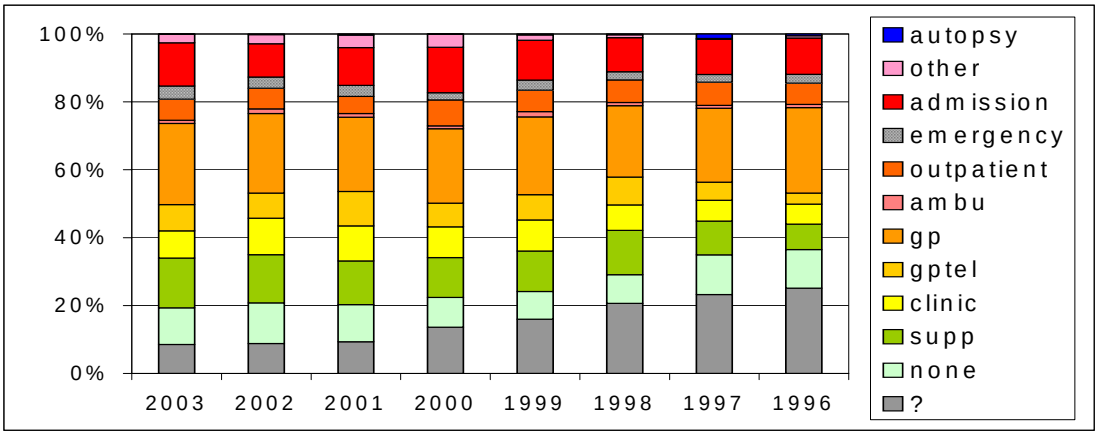


Figure 7. Level of medical intervention for AEFI 1996-2003

6.6 Sex Distribution

Over the years more boys have been reported than girls have. Gradually this has "normalised". In 1994 and before reports concerned boys in 60% of cases, with a gradual decrease from 1995 to 1998 with then stabilisation to 54% for 1998, 1999 and 2000. For 2001 reports concerned in 51% of cases boys consistent with the composition of the cohorts. In 2003, 52% of the reported events concerned boys, equal to 2002 (table 11 and figure 8). Distribution over the different events ranged from 42% boys for discoloured legs to 60% boys with atypical attacks, with events with less than 40 reports excluded. Of 17 children the sex is not known. Under unknown are several cluster reports of minor illness, local reactions and some unsubstantiated rumours. See for specifics on the events and subdivision, the respective categories under paragraph 6.8.

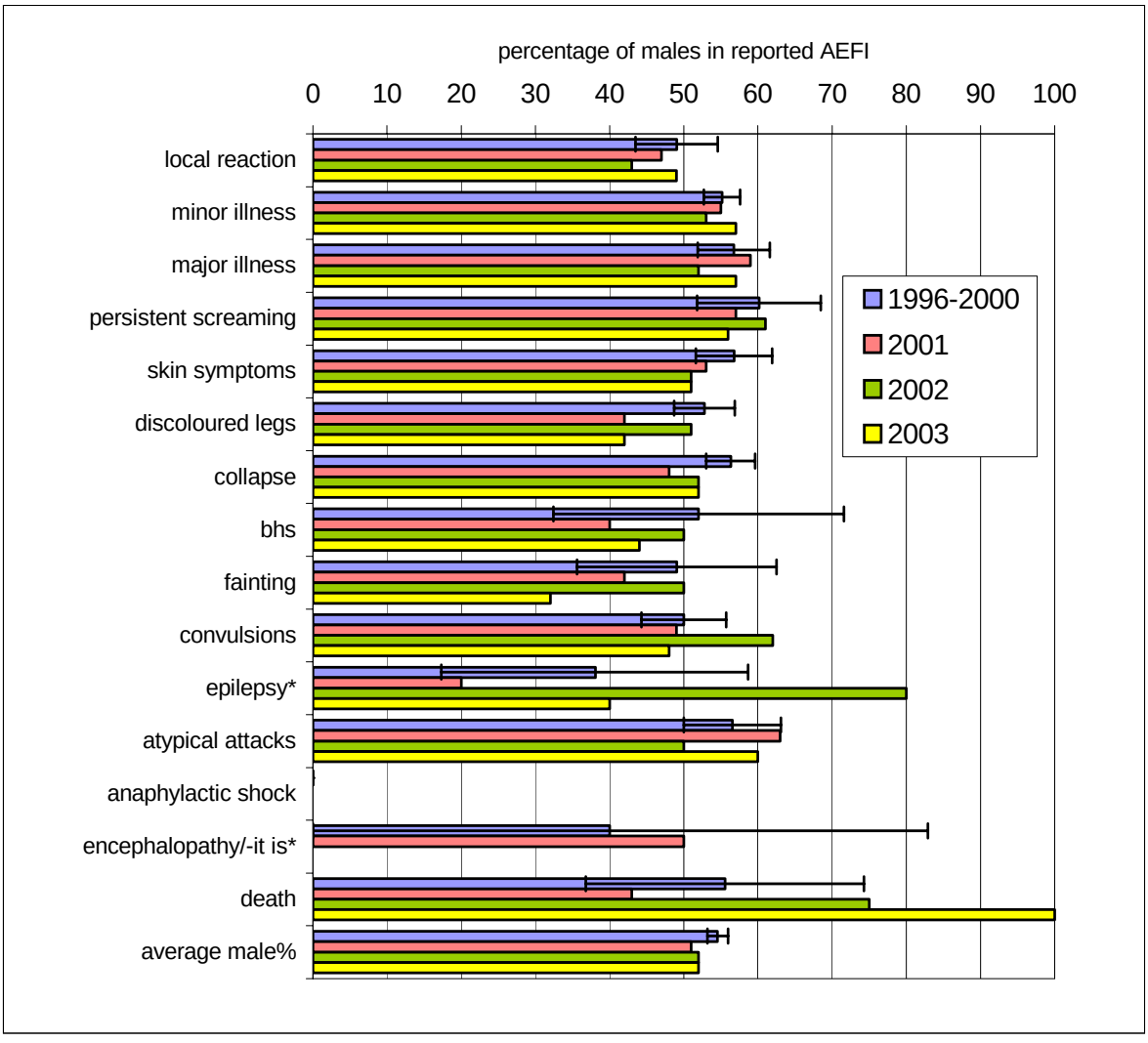


*Figure 8. Events and sex ratio in reported AEFI in 2003 compared to 2002, 2001 and to 1996-2000 with confidence intervals (proportional with exact distribution for *)*

Table 11. Events and sex of reported AEFI in 1998 - 2003

event ⇓		sex⇒	m%	1998 total	m%	1999 total	m%	2000 total	m%	2001 total	m%	2002 total	m%	2003 total
local reaction			52	69	51	89	47	75	47	90	43	120	49	123
general illness		minor	53	405	56	373	57	366	55	447	53	417	57	460
		major	58	85	52	111	60	106	59	74	52	112	57	119
persistent screaming			66	29	58	34	54	39	57	49	61	46	56	55
skin symptoms			58	75	60	85	51	75	53	73	51	104	51	104
discoloured legs			56	125	55	130	52	126	42	175	51	137	42	134
faints	collapse		51	158	54	221	56	221	48	268	53	270	52	210
	BHS		50	4	0	5	60	5	40	5	50	8	44	9
	fainting		55	12	5	18	33	13	42	20	50	19	32	25
fits	convulsions		52	65	49	77	44	63	49	56	62	45	48	70
	epilepsy		33	3	33	3	14	7	20	10	80	5	40	5
	atypical attacks		57	65	53	43	60	42	63	55	50	41	60	57
anaphylactic shock			-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis			-	-	0	1	100	1	50	2	-	-	-	-
death			40	5	86	7	67	3	43	7	75	8	100	3
total			54	1100	54	1197	54	1142	51	1331	52	1332	52	1374

6.7 Causal Relation

Events with (likelihood of) causality assessed as certain, probable or possible is considered adverse reactions. In 2003, 78% of the reports were adverse reactions, a little lower than in 2002 and 2001 (80% and 82%). For 2000, 1999, 1998 and 1997 these percentages were 79%, 84%, 80% and 80% with exclusion of the non-classifiable events. The other events were considered coincidental events with improbable or absent causal relation with the vaccinations. 16 Notifications were not classifiable (1.2%).
There are great differences in causality between the different event categories, but over the years very consistent (table 12 and figure 9). See for description and more detail the specific paragraphs under 6.8 and discussion in chapter 7.

Table 12. Causality and events of reported AEFI in 2003

event ⇓		causality⇒	certain	probable	possible	improbable	non classifiable	total	(% AR*)
local reaction			72	33	17	-	1	123	(100)
general illness		minor	-	183	149	122	6	460	(73)
		major	-	17	47	52	3	119	(55)
persistent screaming			-	55	-	-	-	55	(100)
skin symptoms			-	3	35	63	3	104	(38)
discoloured legs			-	114	14	6	-	134	(96)
faints	collapse		-	188	14	7	1	210	(97)
	BHS		-	6	-	3	-	9	(67)
	fainting		-	22	3	-	-	25	(100)
fits	convulsions		-	12	35	22	1	70	(68)
	epilepsy		-	-	-	5	-	5	(0)
	atypical attacks		-	8	33	15	1	57	(73)
anaphylactic shock			-	-	-	-	-	-	(-)
encephalopathy/-itis			-	-	-	-	-	-	(-)
death			-	-	-	3	-	3	(0)
Total 2003			72	641	347	298	16	1374	(78)

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

For MMR vaccination 59% of the 222 reported adverse events were considered adverse reactions in 2003. This is in the range of 2002, 2001 and 2000 (60%, 57% and 46%, respectively) but lower than in 1999 (65%).
For DTP, DPTP, Hib, aK, MenC and HepB vaccinations, in 72% of the reports possible causal relation was assessed, lower than in previous years (for 2002, 2001, 2000 and 1999 these were 81%, 85%, 82%, and 85%, respectively).

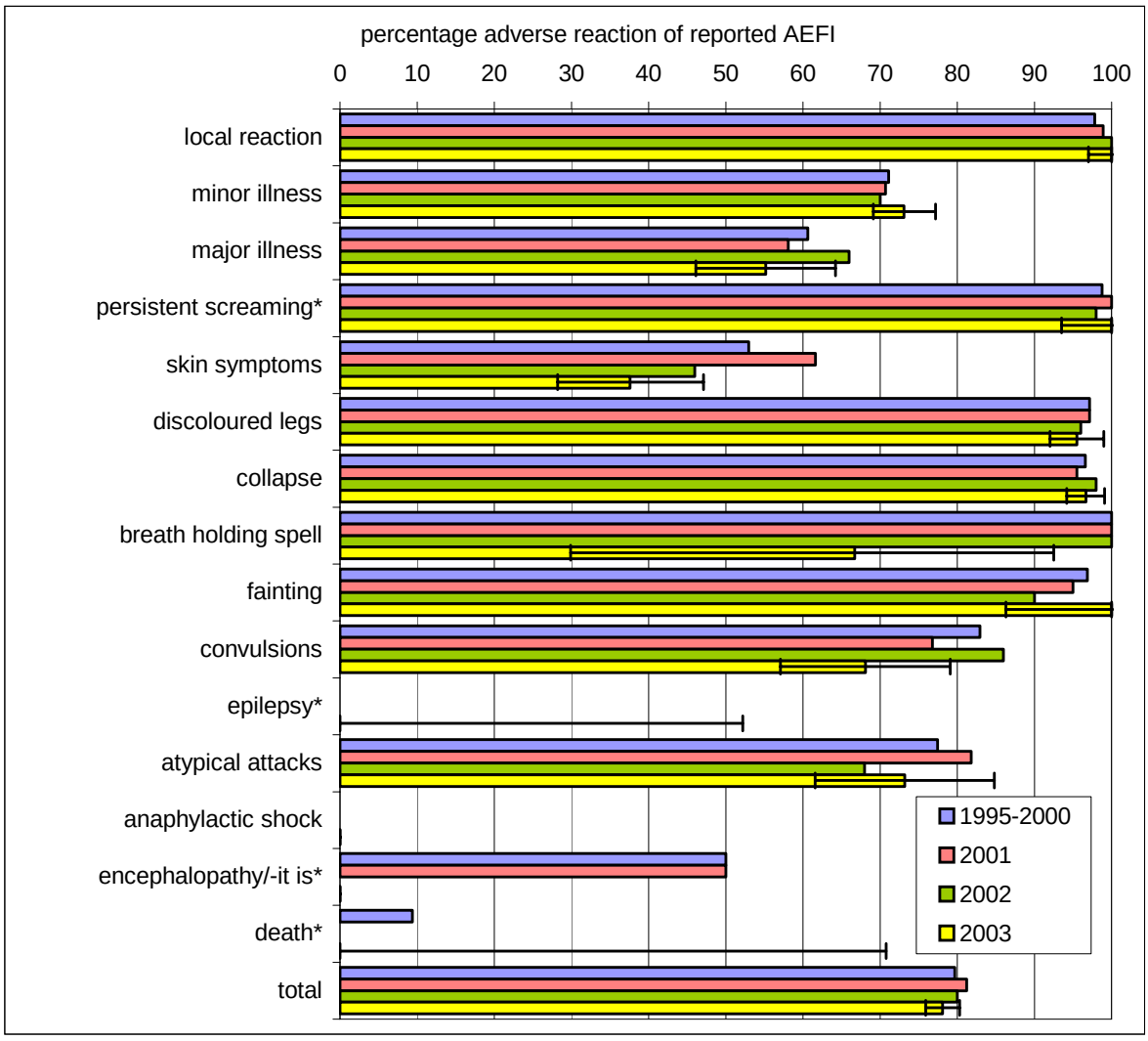


Figure 9. Causality and events of reported AEFI in 2003 compared to 2002, 2001 and 1995-2000 (with 95% confidence intervals, proportional with exact approximation)*

6.8 Categories of Adverse Events

Classification into disease groups or event categories is done after full assessment of the reported event. Some disease groups stay "empty" because no events were reported in 2003.

6.8.1 Local reactions

In 2003, 123 predominantly local reactions were reported in approximately equal frequencies after DPTP/Hib or DTP vaccinations (table 13). All reported local events were considered reactions, i.e. certainly, probably or possibly causally related with the vaccination. One report could not be classified because of missing information (table 12).
The majority of the reported local reactions (100) were mild or moderate. Of these, 23 reports were considered so-called major local reactions because of size, severity, intensity or duration. Common inflammation was most prevalent (75 of which 13 major). The 24 atypical local symptoms (two major) were some kind of local rash or discoloration, possible infection, (de)pigmentation, haematoma/fibrosis, only swelling, itch or pain or combination of atypical symptoms. 12 Children (two major) had marked reduction in use of the limp with mild or no signs of inflammation. This is booked separately as "avoidance behaviour". Avoidance behaviour was also part of other reactions in five cases.

Table 13. Local reactions and vaccines of reported AEFI in 2003 (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)	menc (major)	other (major)	2003 (major)	2002 (major)	2001 (major)	2000	1999	1998
moderate/ pronounced	19(4)	6(1)	7[a](0)	9(1)	1(0)	1(0)	18(6)	12(1)	1(0)	1(0)	75(13)	54(8)	34(5)	36	39	38
absces[s]	-	1[b](1)	3[a](3)	2(2)	-	-	-	-	-	-	6(6)	8 (8)	13(13)	9	11	9
pustule	-	-	-	-	-	-	-	-	-	-	0	1(l)	3(3)	nr	nr	nr
atypical reaction	4[a](2)	4(0)	1[a](0)	4(0)	-	-	8(0)	3(0)	-	-	24(2)	31(3)	22(1)	25	32	22
haematoma	-	1(0)	-	1(0)	-	-	-	-	-	-	2(0)	2(1)	6(1)	nr	nr	nr
nodule	-	1(0)	1(0)	2(0)	-	-	-	-	-	-	4(0)	17(1)	6(2)	nr	nr	nr
avoidance	3(0)	-	1(0)	6(2)	-	-	2(0)	-	-	-	12(2)	7	6(0)	5	7	nr
total (major)	26(6)	13(2)	13(3)	24(5)	1(0)	1(0)	28(6)	15(1)	1(0)	1(0)	123(23)	120(22)	90(25)	75(21)	89(22)	69(15)

[a] once with hepB
[b] with prior bcg

Four of the six abscesses were drained surgically and the two others drained spontaneously. To our information four times cultures were taken, three positive for strepAi. The fourth culture was in the end positive for mycobacterium bovis (BCG strain) disseminated from BCG vaccination site (neonatal). All abscesses were one-sided, once DPTP site, once HepB site, twice DPTP-Hib site and once either Hib or DPTP and the others undecided either DPTP or Hib. No faulty procedures were revealed.

6.8.2 Systemic symptoms

Events that are not classifiable in one of the other specific categories above or below are listed under general illness with depending on severity subdivision in minor or major.

Minor general illness

In 460 children the complaints were considered minor illness in 2003. After the step up in 1998, considered mainly due to the stronger pertussis component in use, the reporting rates

for minor illness have not been significantly different (taking into account the birth cohort vaccine coverage and additional vaccines in the programme). In 2003, 27% of reports were considered to have improbable causal relation with the vaccination, a little less than in 2002 (30% with 27%, 33% and 26-28% for 2001, 2000 and 1999-1996). See table 14 and figure 9. 75% Of reported events concerned the scheduled DPTP/Hib vaccinations, most frequently events following the first dose, with relative share more or less stable over de last five years (table14). For comparison the numbers of 1994-2002 are included.

Table 14. Minor illness and vaccines of reported AEFI in 1994-2003

scheduled vaccine ⇓	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	(%AR*)
dptp/hib1	104	102	85	100	117	102	120	158	141	153[a]	(91)
dptp/hib2	53	54	47	53	81	75	53	65	72	73[b]	(79)
dptp/hib3	37	46	34	42	60	58	45	56	41	52[c]	(54)
dptp/hib4	13	27	32	23	54	60	55	63	58	65	(71)
dptp/hib?	nr	3	1	2	6	5	1	1	3	2[d]	(33)
dptp/hib+mmr1	nr	2	3	1	-	2	2	3	3	1[d]	(100)
mmr1/menC	20	31	32	22	62	55	54	63	51	78[f]	(64)
dtp5+aK	3	6	9	3	11	7	13	16	20	11[g]	(45)
dtp6/mmr2	5	9	1	7	12	8	23	15	8	8	(63)
menC	-	-	-	-	-	-	-	-	17	14[h]	(0)
other	7	-	-	1	2	1	-	7	3	4[i]	(75)
total	242	280	244	254	405	373	366	447	417	460	(73)

* percentage AEFI considered adverse reactions

[a] 12 times with hepB, three times dptp only and once hib only
[b] once with hepB and three times dptp only
[c] five times with hepB and once hepB only
[d] once dptp only
[e] with menC
[f] 19 times mmr only (three mmr0) and 59 times with menC (once mmr0)
[g] once dptp only, once dptp with menC and nine times dtp with aK
[h] once mencevaxACWY and 13 times menC campaign
[i] once hepB, once bcg, once yellow fever and hepA, once rabies and rabies immunoglobulins

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

Fever is the most frequent reported symptom with 100 times the main (working) diagnosis. In all but 16 cases the fever was considered possibly causally related (one non-classifiable report). Body temperature was 84 times 38.5-<40.5°C, five times prolonged, eight times not measured and twice low grade fever (37.5-<38.5°C). Fever was the main accompanying symptom in other (working)diagnoses 212 times (67 times 37.5-<38.5°C, 129 times 38.5-<40.5°C, 16 times not measured).

In 2003 pallor and/or cyanosis was the prevailing symptom in 89 reports in all but three judged to be causally related; in 78% (69) pallor/cyanosis followed the first DPTP/Hib vaccination. Another 43 times pallor/cyanosis was an accompanying symptom.

Crying was the main feature in 59 reported cases predominantly following the first two vaccinations, 43 times vehement and four times prolonged and 12 times unusual. Crying was often pronounced in the other events also (160) or groaning (24).

Chills were sometimes the (working)diagnosis (18), as were (sleeping) jerks or myoclonics (21), with or without fever, as often as main working diagnosis as in accompanying

symptoms. Apathy, drowsiness or sleepiness was the main feature in 13 cases and gastric-intestinal complaints 19 times. Respiratory tract symptoms like common cold, tonsillitis, pseudocroup, pneumonia, otitis, asthma, bronchitis etceteras, were frequently diagnosed (20). Of the 68 children with (possible) rash illness 31 were considered to be "vaccinitis" following MMR and all of the other 37 were judged to be coincidental events. See for further symptoms and causality table 15.

Table 15. Main (working) diagnosis or symptom in category of minor illness of reported AEFI in 2003 (with number of adverse reactions)

symptom or diagnosis	2001	(AR*)	2002	(AR*)	2003	(AR*)	symptom or diagnosis	2001	(AR*)	2002	(AR*)	2003	(AR*)
fever	87	(70)	70	(54)	100	(79)	pallor and/or cyanosis	77	(75)	79	(76)	89	(86)
low temperature	5	(5)	2	(2)	2	(2)	abnormal level liver enzymes	1	(0)	1	(0)	1	(0)
crying	51	(48)	51	(47)	59	(55)	rash (illness)	25	(3)	21	(0)	37	(5)
groaning	1	(1)	1	(1)	-	(-)	vaccinitis	21	(21)	20	(20)	31	(31)
irritability	5	(3)	4	(2)	-	(-)	parotitis	2	(2)	3	(3)	-	(-)
meningismus	3	(1)	1	(0)	-	(-)	swelling face/hands/feet/?	6	(4)	4	(2)	3	(1)
hypertonia	1	(1)	1	(1)	2	(1)	lymphadenopathy	3	(0)	2	(1)	1	(1)
myoclonics	20	(18)	16	(15)	21	(19)	arthralgia/arthritis/coxitis/limping/ falling/disbalance/pain in limbs	6	(3)	6	(2)	8	(3)
chills	14	(12)	12	(11)	18	(17)	allergy/atopy	1	(0)	2	(1)	1	(0)
bulging fontanel	1	(1)	-	(-)	2	(1)	feeding problems	8	(4)	4	(1)	1	(0)
headcircumference ⇑⇑	-	(-)	1	(0)	-	(-)	anaemia	-	(-)	1	(0)	-	(-)
listlessness/fatigue	3	(1)	4	(2)	7	(2)	vomiting/nausea	6	(4)	4	(2)	4	(3)
drowsiness	4	(3)	2	(2)	5	(3)	stomatitis/abscess	1	(0)	3	(0)	1	(0)
prolonged/deep sleep	9	(9)	7	(7)	8	(8)	constipation	-	(-)	2	(0)	1	(0)
behavioural problem/-illness	13	(6)	19	(11)	6	(4)	gastro-enteritis/diarrhoea	13	(1)	20	(5)	14	(3)
sleeping problems	2	(1)	2	(2)	2	(2)	myoglobinuria?	2	(2)	7	(7)	-	(-)
apnoea /low oxygenation	-	(-)	2	(2)	2	(1)	epidiydimitis/urinary tract infection/haematuria	1	(0)	1	(0)	-	(-)
asthma (attack)/cara	7	(0)	1	(0)	2	(0)	epistaxis	1	(0)	-	(-)	-	(-)
airway infection	9	(0)	12	(0)	8	(0)	headache/migraine/dizziness	2	(1)	4	(2)	4	(1)
cough	4	(1)	6	(0)	4	(0)	turning eyes	1	(1)	-	(-)	-	(-)
dyspnoea/wheezing	4	(3)	2	(0)	3	(1)	nystagmus/squint/anisocoria abducens paralysis/conjunctivitis	2	(0)	4	(1)	1	(0)
pseudocroup	2	(0)	1	(0)	-	(-)	heart murmur	-	(-)	-	(-)	1	(0)
tonsillitis/cold	3	(0)	-	(-)	-	(-)	lying still/frozen	9	(9)	6	(6)	4	(3)
otitis	2	(0)	1	(0)	3	(0)	transient episode undefinable	3	(1)	1	(0)	-	(-)
infectious disease	2	(0)	1	(0)	2	(0)	not specified	4	(1)	3	(1)	2	(0)
							total minor events	447	(316)	417	(288)	460	(332)

* number of adverse reactions

Of the reported AEFI 87 concerned MMR vaccine with in 55 cases a possible causal relation, of which ten times attributed to simultaneous other vaccines. Thus in 53% of the reports of minor general illness following MMR the event was considered adverse reaction to MMR. For the other vaccine combinations this was the case in 66%, with two events not classifiable.

Major general illness

In 2003, 119 reports were classified as major general illness, compared to 112 in 2002, 74 in 2001, 106 in 2000, 85 in 1998 and 111 in 1999 (table 16). The distribution in the major illness group is more even over the scheduled vaccines than in the minor illness group. Overall, 64 events were considered adverse reactions (54%), lower than in 2002 (65%, with for 2001 and 2000 both 58%). On average from 1995-2000 reported major illness had

causality inferred in 60% (range 52%-70%). See table 17 and figure 8. In the 52 AEFI considered to be chance occurrences (three non-classifiable) with the time interval not plausible and/or other causes established.

Table 16. Major illness and vaccines of reported AEFI in 2003 (adverse reactions)

diagnosis⇓ vaccine⇒	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	mmr1/ menC	dtp5/aK	dtp6/mmr2	menC	other	total	(AR*)
high fever	10	9	4	20[b]	7	1	-	1	-	52	(44)
chills/myoclonics	-	-	1	1	1	-	-	-	-	3	(3)
hypertone dehydration/IBD	-	-	-	-	1[c]	-	-	1	-	2	(0)
pneumonia	-	-	-	-	1	-	-	-	-	1	(0)
apnoea / decrease in oxygenation	2	1	-	-	-	-	-	-	-	3	(2)
meningitis/septicaemia	1	1	1	-	-	-	-	-	-	3	(0)
rash illness	-	-	1	2	-	1[f]	-	-	-	4	(0)
vaccinitis	-	-	-	-	1	-	-	-	-	1	(1)
Henoch schonlein	-	-	-	-	-	-	-	1	-	1	(0)
arthritis/osteomyelitis	1	1	-	1	3[d]	1	-	2	-	9	(2)
lymphadenitis colli/abscess	-	-	-	-	1[e]	-	-	1	-	2	(0)
ITP	1	4	-	3	11[e]	3	2	1	1[h]	26	(11)
ataxia	-	-	-	-	-	1	-	-	-	1	(0)
diabetes mellitus	-	-	1	-	2	-	1	-	-	4	(0)
metabolic disease (derangement)	-	-	-	1	-	-	-	-	-	1	(1)
anorexia and weight loss	-	-	-	-	-	-	-	1	-	1	(0)
hepatitis b	-	-	-	-	-	-	-	-	1[k]	1	(0)
hemiplegia	1[a]	-	-	-	-	1[g]	-	-	-	2	(0)
optic neuritis / atrophy	-	-	-	-	-	-	-	2	-	2	(0)
Total 2003 (adverse reactions)	16	16	8	28	28	8	3	10	2	119	(64)

* number of AEFI considered adverse reactions

[a] once with hepB
[b] once dptp only and once with mmr0
[c] mmr0 with hepb, yellow fever and bcg
[d] once once mmr only and once mmr0.
[e] once mmr only
[f] once dptp and mmr catch up dose
[g] once dtp only
[h] bcg
[k] hepb

33 Reports concerned MMR with in 21 cases (66%) assessed causality and none of the events attributable to the other vaccines given simultaneously. One event was non-classifiable. These percentages were 45% in 2002 and 48%, 41% and 43% in 2001, 2000 and 1999. For the other vaccines or combinations 43 (38%) reported events were considered to be possible adverse reactions with two events non-classifiable, compared to 69% in 2002 and 60%, 66% in 2001 and 2000 and 75% in both 1998 and 1999. See also table 17.

Very high fever (≥40.5°C) was the working diagnosis in 52 cases with in one case intermittent fever over a longer time. In all but eight cases causality was inferred. In the other events in this category very high fever was present in 8 cases, in four reports because of infectious disease and judged to be coincidental. The other four cases very high fever was present in the so-called vaccinitis following MMR1 (1) and chills/myoclonics (3). In other event categories there was very high fever in another 12 cases, mainly in febrile convulsions (7) and also in atypical attacks (5). These are not listed separately under this major illness category, since the fever was considered part of the syndrome.

ITP (Idiopathic/Immunologic Thrombocytopenic Purpura) was reported 26 times: three times only through passive surveillance, 22 times only by the paediatric surveillance unit (NSCK),

and once first through passive surveillance and later also by NSCK. Of the 13 cases following MMR1 11 were considered possibly causally related. The other two were considered chance occurrences. 13 Reported cases of ITP followed other vaccines; all were considered chance occurrences. We will report separately on this active surveillance study on ITP. One child had metabolic/hereditary disorder in which derangement was possibly caused by the fever of the vaccine. In three preterm children there was possibly apnoea and/or decrease in oxygenation and causal relation with the vaccination was judged possible in two. In two children with (reactive) arthritis causal relation with the MMR vaccine could not be ruled out. All other events in this category have been assessed very carefully but in none inference of causal relation with the vaccination appeared warranted because of time interval and/or other established causes.

Table 17. Major illness and causal relation of reported AEFI in 2003

diagnosis⇓ causality⇒	certain	probable	possible	improbable	unclassifiable	total	(AR%)
high fever	-	15	29	8	-	52	(85)
chills/myoclonics	-	2	1	-	-	3	(100)
hypertone dehydration/IBD	-	-	-	2	-	2	(0)
pneumonia	-	-	-	1	-	1	(0)
apnoea / decrease in oxygenation	-	-	2	1	-	3	(67)
meningitis/septicaemia	-	-	-	3	-	3	(0)
rash illness	-	-	-	4	-	4	(0)
vaccinitis	-	-	1	-	-	1	(100)
Henoch schonlein	-	-	-	1	-	1	(0)
arthritis/osteomyelitis	-	-	2	6	1	9	(25)
lymphadenitis colli/abscess	-	-	-	2	-	2	(0)
ITP	-	-	11	13	2	26	(46)
ataxia	-	-	-	1	-	1	(0)
diabetes mellitus	-	-	-	4	-	4	(0)
metabolic disease (derangement)	-	-	1	-	-	1	(100)
anorexia and weight loss	-	-	-	1	-	1	(0)
hepatitis b	-	-	-	1	-	1	(0)
hemiplegia	-	-	-	2	-	2	(0)
optic neuritis / atrophy	-	-	-	2	-	2	(0)
total 2003	-	17	47	52	3	119	(54)

6.8.3 Persistent Screaming

In 2003, 55 children with persistent screaming were reported (in 1994-2002 respectively 37, 22, 16, 26, 29, 34, 39, 49 and 46). The reported persistent screaming seems age/dose dependent, as has been noticed in former years (see table 9). Local symptoms were pronounced in only in 12 cases, of which nine mainly had (presumed) pain at the injection site and once the child avoided moving the legs more or less completely. Some of the children had both sided local reactions. Additional symptoms were restlessness, feeding difficulty, and pallor. Parents were usually desperate and 11 contacted the family physician and one was admitted in hospital. We did not record the degree of intervention in eight cases, however (table 9). In all cases the event was considered to be causally related with the vaccinations (table 11). See also under discussion, chapter 7.

6.8.4 General skin manifestations/phenomenon

In 2003 skin symptoms were the main or only feature in 104 reports, equal to 2002. (74, 75,

85, 75 and 73 in 1997, 1998, 1999, 2000 and 2001). Discoloured legs are not included but are categorised separately. The numbers are considerably higher than in prior years with increase mainly in reported AEFI following MMR1, DTP5/aK and single menC vaccinations. The number of reports considered adverse reactions was 38, a little lower than in 2002 and 2001 with 47 and 45, respectively. See table 18.

Table 18. Skin symptoms and vaccines of reported AEFI in 2003 (adverse reactions)

vaccine⇒ / symptoms⇓	dptp hib1	dptp hib2	dptp hib3	dptp hib4	mmr1 menc	dtp5 ak	dtp6 mmr2	menc	other	total	(AR*)
angio-oedema/swelling	3[a]	2	1	-	2[b]	-	1	-	-	9	(5)
exanthema	11	11	9[c]	6[d]	10[e]	3	3	2	1	56	(22)
lymphadenopathy	-	-	-	-	1	-	-	-	-	1	(0)
erythema arm (vaccine in leg)	-	-	1	1	-	-	-	-	-	2	(0)
herpes zoster	-	-	-	-	1[b]	-	-	-	-	1	(1)
blisters	-	-	-	-	-	1	-	-	-	1	(0)
aphthae	-	-	-	-	-	1	-	-	-	1	(0)
urticaria	2	1	2	2	2[f]	3	1	-	-	13	(3)
eczema (increase)	3	1	2	3[h]	3[g]	-	-	1	-	13	(4)
petechiae	3[c]	-	-	-	-	-	1	-	-	4	(3)
striae	-	-	-	-	-	-	-	1	-	1	(0)
(de)pigmentation	-	-	1	1[h]	-	-	-	-	-	2	(0)
total 2003	22	15	16	13	19	8	6	4	1	104	(38)

* number of AEFI considered being adverse reactions
[a] once with hepB and once dptp only
[b] once mmr only
[c] once with hepB
[d] once dptp only
[e] three times mmr only (once mmr0)
[f] once mmr0 only
[g] twice mmr only
[h] once dtp only

One child had a major skin event, herpes zoster infection. This eruption started 6.5 days following MMR vaccination was very painful and lasted for months. All other reports were of minor skin manifestations.
Exanthema, urticaria and (increased) eczema were the most frequent symptoms, amounting to 77%. Nine times there was noted vasomotor swelling/angio-oedema or swelling of the face or hands. There were four children with petechial rash on upper body and/or face. Children with petechiae on the legs only are categorised under discoloured legs.
19 Cases concerned MMR1 (twice mmr0) in 8 without simultaneous menC. Eight times (possible) causal relation with MMR, three times attributable to either vaccine and once to the other. In one out of the six times MMR was combined with DTP there was a possible causal relation caused by either vaccine. This resulted in possible causal relation with MMR in 48% (equal to 2002) with rashes in the second week after the vaccination (without systemic symptoms) or on the day of vaccination when causal relation could not be ruled out. The other events were not considered causally related with the vaccination, because of inconceivable time interval and/or other cause. For the other vaccines or combinations, possible causal relation was assessed in 30 out of 93 events (32%, compared to 45% in 2002). See table 19.

Table 19. Skin symptoms and causal relation of reported AEFI in 2003

causality⇒ / symptom⇓	certain	probable	possible	improbable	unclassifiable	total	(%AR*)
angio-oedema/swelling	-	-	5	4	-	9	(56)
exanthema	-	3	19	33	1	56	(40)
lymphadenopathy	-	-	-	1	-	1	(0)
erythema arm (vaccine in leg)	-	-	-	2	-	2	(0)
herpes zoster	-	-	1	-	-	1	(100)
blisters	-	-	-	1	-	1	(0)
aphtha	-	-	-	1	-	1	(0)
urticaria	-	-	3	10	-	13	(23)
eczema (increase)	-	-	4	8	1	13	(33)
petechiae	-	-	3	1	-	4	(75)
striae	-	-	-	-	1	1	(0)
(de)pigmentation	-	-	-	2	-	2	(0)
total 2002	-	3	35	63	3	104	(38)

* percentage of AEFI considered being adverse reactions

6.8.5 Discoloured legs

Starting from 1995, discoloured legs are 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. From 2001 onward also swollen limps with or without discoloration after the fifth dose of DTP an aK are included. In 2003, 134 reports were received (137 in 2002 137, with in 2001 and 2000 175 and 126 reports in 2001 and 2000; table 19). Of these 29 were blue legs (23 double-sided), 51 red legs (30 double-sided) and 24 purple legs (21 double-sided). 34 Cases had one-sided discoloration, two concerning the DPTP leg, one the Hib leg, one the DTP arm and two the aK arm, but in four cases this could not be decided. In total, 48 children had petechiae, including 26 reports without noted prior discoloration of the legs (35 times both sided). Leg petechiae with or without prior discoloration was reported 31, 30, 33, 28, 31, 38 and 38 times in 1996, 1997, 1998, 1999, 2000, 2002 and 2002, respectively.
About 25% (33) of the reported children had also fever, one ≥40.5°C and listed also in the major general illness category. An additional 30 had low-grade fever (≥37.5-<38.5°C). Over 74% of the children exhibited fierce crying of whom three cried over extended time, not exactly defined (none of these has been categorised under persistent screaming). Injection site reactions, if any were not pronounced, but 26 times severe pain (once extreme) was noted/presumed, 18 times without any other signs of inflammation. Seven children had also collapse reaction. These compound reports are grouped under collapse as well. 17 children were reported with recurrent discoloured legs after subsequent vaccination. Distribution over the different vaccine doses remained the familiar pattern over the years with reports most frequent after the first DPTP/Hib vaccinations (46%) and decreasing in number with dose number and age. Causal relation with the vaccines was inferred in all but six cases. See table 11 and figure 6.

Table 20. Discoloured legs and vaccines of reported AEFI in 2003

vaccine⇒ symptoms⇓	dptp hib1	dptp hib2	dtpt hib3	dptp hib4	mmr1 menc	dtp5 ak	petechiae	total 2003	2002	2001	2000	1999	1998	1997
blue legs	13	11	3	1	1[e]	-	3	29	26	31	23	17	25	23
red legs	19	18[c]	8[d]	6	-	-	11	51	40	63	46	55	56	38
purple legs	13[a]	8	3	-	-	-	8	24	43	56	47	30	30	23
petechiae only	8[b]	11	6	-	1	-	26	26	23	22	9	28	14	11
swollenlimb	-	-	-	-	-	4	-	4	5	3	nr	nr	nr	nr
total	53	48	20	7	2	4	48	134	137	175	126	130	125	95

[a] four times with hepb
[b] once also hepb
[b] once dptp only
[d] once with menC and once dptp only
[e] once mmr only

6.8.6 Faints

In this event category, collapse (hypotonic-hyporesponsive episode, HHE), syncope (fainting) and breath holding spells (BHS) are listed (table 21).

Table 21. Faints and vaccines of reported AEFI in 2003

vaccine⇒ event⇓	dptp hib1	dptp hib2	dptp hib3	dptp hib4	mmr1 menc	dtp5 aK	dtp6 mmr2	menc	other	Total 2003	2002	2001	2000	1999	1998	1997
collapse	147[a]	37	19	7	-	-	-	-	-	210	270	268	221	221	158	145
bhs	6	-	1	1[b]	1	-	-	-	-	9	8	5	5	5	4	4
fainting	-	-	-	-	1	17[b]	3[c]	2	2[d]	25	19	20	13	18	12	6
total	153	37	20	8	2	17	3	2	2	244	297	293	239	244	174	155

[a] 11 times also hepB
[b] once dtp only
[c] once mmr only
[d] once hepb and once pneumo23

In 2003 there were 210 collapse cases reported, somewhat lower than in 2002 and 2001 (270 and 268), in absolute numbers the same level as 2000. Also nine children were reported with BHS; the children turned blue, after stopping to breathe in expiration when fiercely crying or other stimuli, with a very short phase of diminished responsiveness and no limpness or pallor. 25 Children were reported fainting.
The distribution of collapse over the different scheduled vaccines is, as we described before, in the majority of cases after the first DPTP/Hib vaccinations (over 70%) and numbers diminishing with dose number and age [32,40,43]. See for further information under introduction, chapter 1, and discussion, chapter 7. In 2003 there were eight children with recurrent collapse reported (versus 12 in 2002, 18 in 2001 and 5 in 2000), some of them with rather incomplete episodes. In seven children with single collapse reactions the collapse was assessed as not related because of the too long time interval and/or other causes (compared to 6 in 2002, 9 in 2001 and 4 in 2000). See also tables 11 and 12 and figures 7 and 8 for sex distribution and causality.

6.8.7 Fits

In this category (febrile) convulsions and epileptic seizures find a place. Also “atypical attacks” in case definite diagnosis could not be made and convulsion could not be fully excluded either, are listed here. (See also paragraph 5.5)
Most reported convulsions were febrile (64 out of 70), occurring predominantly after the fourth DPTP/Hib (24) and MMR1/MenC (32) vaccinations. Six non-febrile convulsions were reported. The reported atypical attacks were also most frequent after the vaccinations in the around one year olds (table 22). Fits (convulsions or atypical attacks) at the younger ages were less frequently accompanied by fever than at later doses/older ages, more so in case of convulsions than in the atypical attacks. Altogether 12 children had fever of 40.5°C and over, five times in children with atypical attacks and seven times with convulsions five times considered not causally related. In all but three, this very high fever occurred in the one year-olds (5 times fourth DPTP/Hib and 3 times MMR1 and once Hib). See table 11 for sex distribution and table10 for degree of intervention.

Table 22. Fits and vaccines of reported AEFI in 2003

vaccine⇒ / event ⇓	dptp hib1	dptp hib2	dptp hib3	dptp hib4	mmr1 menc	dtp aK	dtp6 mmr2	menc	total 2003	2002	2001	2000	1999	1998	1997
febrile convulsion simple	-	1	2[a]	10	14	-	-	1	28	22	26	29	42	39	27
complex	1	-	-	10[b]	12	-	-	-	23	20	21	26	24	17	18
tonic	-	-	-	2	-	-	-	-	2	-	2	1	1	2	1
atypical/not specified	-	-	-	2	6	1	1	1	11	3	2	3	4	3	6
non febrile convulsion	-	1	1	1	3	-	-	-	6	-	5	4	6	4	5
epilepsy	2	1	1	-	-	-	1	-	5	5	10	7	3	3	5
atypical attack	4	9	9[a]	19[c]	14[d]	1	-	1	57	41	55	42	43	65	45
total	7	12	13	44	49	2	2	3	132	91	121	112	123	133	108

[a] once also hepB
[b] once dptp only and once dptp-hib with mmr and menC
[c] once hib only
[d] three times mmr only

64 Convulsions were definitely with fever, with in 44 were possibly due to the fever by the vaccination and considered adverse reaction. 19 Convulsions with fever were not considered to be causally related, as there was other cause established and/or an implausible time interval with the vaccination (eight following MMR1/menC, nine after DPTP/Hib4 and one following menC in the campaign). One report was not classifiable because of missing information (MMR1). See also table 12. Of the non-febrile convulsions three were considered possibly caused by the vaccine the other three considered chance occurrences including one child with epilepsy and an increase in seizures.
Five children with epilepsy were reported, of which one had (possible) West syndrome. In none of the children (fever caused by) the vaccine was regarded as trigger.
57 Reports were classified as atypical attacks, with in 41 cases possible causal relation with the vaccination. In this subcategory there were ten children with possible chills and/or myoclonics. Six children had possible breath holding spells, one choked, and ten children were hypertonic and/or limp. The other 14 the symptoms were very aspecific. None of the children fulfilled the case definitions for collapse or convulsion.

In 2003 MMR was involved in 52 reports, 37 times with simultaneous menC, once also with DPTP-Hib, and twice MMR with simultaneous DTP.
34 Times causality was inferred with MMR, once the event was attributed to the other simultaneous vaccine and one event was unclassifiable. Thus there was imputed causal relation of the fits with MMR in 67% (82% in 2002, 73% in 2001 and 57%, 89%, 71% and 71% in 2000, 1999, 1998 and 1997 respectively) and for the other vaccines in 46% of reported cases (62% in 2002, 73% in 2001 and 78%, 87%, 87%, and 77% in 2000, 1999, 1998 and 1997, respectively).

6.8.8 Encephalopathy/encephalitis

In 2003 there were no reports of encephalopathy or encephalitis following vaccination. One child with a brain infarction following vasculitis as post varicella complication with underlying coagulopathy (factor V Leiden deficiency) is booked under major illness.

6.8.9 Anaphylactic shock

There were no reports on anaphylactic shock in 2003. One child known with prior syncope fainted again and had several relapses in the hour after the vaccination. Because of apprehension she was seen in hospital where the event was diagnosed as vasovagal episode. In 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.

6.8.10 Death

In 2003 three children who died following vaccination, were reported (see table 23). These concerned three boys. See the case histories below. Two 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. It should be stressed however that without full post-mortal investigation a definite diagnosis is often not possible.

Child A
A boy of three months old got his second DPTP and Hib vaccinations. He had some diarrhoea since the day before, but was not ill and had no fever. Three and a half hours after the vaccinations he had his bottle but resisted the teat. He turned blue and started vomiting. He appeared not to breathe properly. In panic the parent shook the baby, but he kept vomiting. On advice of the emergency phone staff (112) mouth to mouth was started. After arrival of the ambulance he was intubated and rushed to hospital. There he was re-intubated because of bad position of the tube in the oesophagus, and transported to a university paediatric intensive care unit. The child died the next day. Autopsy revealed signs of intra-ocular haemorrhage and intracerabral bleeding. Also signs of more diffuse brain aphyxia. Cause of death brain injury, caused by shaking and by lack of oxygen (possibly caused by aspiration and the faulty position of the tube). The incident with the vomiting could have been provoked by the vaccination, also be a sign of gastro-enteritis. The vaccines did not cause the death.

Child B

A boy of 16 months old received his first MMR and MenC vaccination. He already had a runny nose and itching, especially at night. From the age of 2.5 months old he suffered from exsudative eczema with itch. After the vaccinations there were no specific systemic symptoms and no local reaction. Three days after, he went to bed a little later than usual, because of a holiday. The next morning he was found dead. At post-mortem a petechial rash was noted over face and arms, apart from the known severe infected eczema. Autopsy did not reveal cause of death. Cultures taken from tissue and usually sterile fluids were positive for both Staphylococcus aureus and B-Haemolytic streptococcus group A. The child died of septicaemia, unrelated to the vaccinations.

Child C

A boy of 14.5 months old received his first MMR en menC vaccination. A week before, the vaccinations were postponed because of fever. This time he was well. Within an hour he developed fever, had chills and looked greyish pale. The GP examined him and concluded "flu" or reaction to the vaccination after conferring with a paediatrician. He became increasingly ill during the evening and the fever got higher and higher. The GP was consulted by telephone and later during the night again. In the early morning he was seen at the night clinic when he had developed petechiae and purpura. He was rushed to hospital and after stabilisation transported to an academic high-care centre. He died after ten days because of complications of septic shock, caused by Meningococcus serogroup B. This infection is not caused by the vaccination, nor aggravated by it. It is possible, however, that the fact that he was vaccinated caused a (fatal) delay because for too long the symptoms were regarded as common adverse effects of the vaccines.

Table 23. Death and vaccines of reported AEFI in 2003

child	sex	age[a]	vaccines	time interval		symptoms/diagnosis	causality[b]	autopsy
				illness	death			
A	m	3m	dptp+hib2	3.5hr	1d	Vomiting, aspiration, shaken baby syndrome, ashyxia with faulty position of the tube and death by brain injury	no	yes
B	m	15m	mmr1+menc	-	3-4d	Bacteriaemia staph-au and strepA	no	yes
C	m	14	mmr1+menc	<1hr	9d	Meningococcus B-sepicaemia	no	no

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

[b] age at vaccination

7 Discussion

The success of the vaccination programme, having brought the target diseases under control, increases the relative importance of side effects [10,11]. This increases the demands on the safety surveillance system like wise. Mere registration and reporting of possible adverse reactions is not enough to sustain confidence in the safety of the programme [58,59,60]. 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 again given special attention. The number and nature of reported adverse events will be discussed in the light of the two new additions to the programme. This is the first full year MenC was included and HepB has been introduced for risk group children born in 2003 (and later). 2003 is the second full year in which all 4-year-olds had the aK booster with their DTP. From March 2003 onwards the simultaneous DPRP+Hib will be replaced by mixed DPTP-Hib administration. Other trends or signals will be discussed [38,39,45].
The increased attention of the public and professionals with regard to the safety of vaccines may have consequences for the willingness to participate in the programme. It may also influence the number and the type of events reported.
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.

7.1 Safety Surveillance of the RVP

Safety surveillance of the vaccination programme seems to be of increasing importance [10,11,61,62,63]. The Dutch system has several strong points. Denominators are known, because the PEA registers all administered vaccines on individual level [50,44,53]. The RVP is embedded in the regular Child Health Care with its near total coverage; therefore the programme is delivered by a relatively small group of specifically trained professionals. It is good professional standard in the clinics to ask after adverse events at the next clinic visit and before administration of the next dose. The operation of a (24-hr) central telephone information service for professionals at RIVM is a most important and efficient tool in obtaining notifications. It also keeps 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. Because of the wide reporting criteria the system allows sensitive signal

detecting of new adverse events or interactions. Trend analysis is possible. The system with mainly nominal reports allows follow up and some other systematic studies, like nested case-control studies [41,64.] Assessing causal relation is essential in monitoring the safety of the vaccination programme [54,62,65,66,67]. Of course, after vaccination does not mean caused by vaccination. Installation of an RIVM expert panel will allow broader scientific assessment in selected cases. Five of the 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 [68]. Also different schedules and/or vaccines and combinations are used.
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 [7,67]. 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 followed intensely there where they are in actual use.
The current enhanced passive surveillance system will need to be supplemented by more active monitoring and systematic studies to test generated signals and hypotheses. 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) [69,70]. The placement of the safety surveillance system at RIVM with its expertise should guarantee high quality assessment of the safety of the RVP.
The current enhanced passive surveillance system performs satisfactory. The strength of the system outweighs the inherent weaknesses. See for further details the subparagraphs below and paragraph 7.5.

7.1.1 Information Service, Reporting Route and Feedback

We hold the telephone service as 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. This low threshold reporting channel has great advantage over written report forms not only because of superior possibility of communication, timeliness and supplementation of data. It is also an important tool for adherence to the programme, to promote proper use of contraindications and it offers guidance to the professionals to ensure adequate vaccination in special circumstances or underlying disorders.
It makes very efficient use of resources, both at the level of RIVM and in the broader perspective of management of the vaccination programme as a whole. Written reports are generally of much poorer quality because of the absense of possibility of clarification. This has been our experience through the years and has been illustrated in the MenC-campaign in 2002 again.[48] The necessary follow-up of these reports is much more time consuming than primary clarification ,verification and supplementation in direct contact. In part this is because every (eventual) type of event has a distinct, different and evolving set of questions,

usually not predictable beforehand. It is like the noble art of proper medical history taking: the given answer and the subsequent re-weighting of the data directs the next question.
Education of potential reporters, while essential, will not yield much gain in efficiency for the type of reports received in a passive surveillance system. One has to bear in mind that adverse events reported in passive surveillance systems are in majority severe, peculiar, unexpected and rare events, and in case of more common events, concern special circumstances or specific underlying problems.They are the exceptions and not the rule. One cannot expect that health care professionals know what specific extra information is needed for every possible specific event, age and vaccine and keep up with all medical literature in this respect. Education which stresses the importance of reporting and explains the type of basic information necessary to keep at hand when reporting, may contribute to further efficiency gains. Awareness that it is necessary to report should be enhanced. Reporting by mail is possible of course but only less than 8% actually report in writing. Apparently reporters favour reporting by telephone since it offers instant opportunity for consultation.
Feedback to the reporters of the final AEFI assessment is important. It should be noted in the child's chart. We will in time supply standardised written feedback forms with RIVM assessment for the reporters, and develop access to report forms on an interactive website if resources allow. This will have to wait till the installation of a robust database however.
E-mail addresses and fax numbers are already available. Follow up of children with reported adverse events is important. We will explore how this feedback to and the follow up from the clinics can be done routinely in a systematic and efficient order. This will increase our knowledge about specific adverse events, risk factors and sequelae and will in turn lead to a safer programme. This information may also be used in educating public and providers.
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 [71,72,73,74]. The RVP communication project of RIVM in close collaboration with other parties has developed factsheets and web based material for parents in spring 2004. It is planned to add more in depth material for professionals. (www.rijksvaccinatieprogramma.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.

7.1.2 Verification and Assessment

In the monitoring of the safety of the vaccination programme, validation and supplementation of information with follow up is considered of utmost importance. A substantial part of supplementation and verification is done in the reporting telephone call. With written notifications this is much more time-consuming and will have to wait until later.
Discrepancy is often quite large between reported symptom/diagnosis and final diagnosis. This discrepancy is partly due to different case definitions, but also because of more detailed further (follow up) information and more specific expertise of RIVM. The value of a detailed account by the parents, especially in case of paroxysmal events, can not be overrated. Careful history taking after the first panic has subsided is of great importance [41,66,75.] Especially

collapse reactions are often reported as something else, like ALTE or near-SIDS, convulsion, anaphylactic shock, allergic reaction, encephalopathy etceteras. This is not as surprising as it may seem. A GP with an average of 30 new-borns a year may come across collapse reactions after vaccination only once in 30-50 years! And for paediatricians also it is a rather rare entity and they feel more confident with other severe illnesses more frequently encountered. One tends to mould symptoms in known diagnostic categories. But on the other hand, reported collapse reaction does not always fulfil the criteria for collapse. Often there is only pallor or only apathy or just drowsiness or excessive sleep/difficulty in awakening and symptoms do not fit the case definition. The same applies, even more so, for reported convulsions.
Skin symptoms tend to cause great concern because of feared anaphylactic reactions following a next dose. Like in former years most children with skin symptoms, even if apparent/occurring in close time relationship with the vaccination, get a subsequent dose without recurrence. Severe anaphylactic reactions have not been known to happen with the vaccines of the RVP. We prefer descriptive low level terms for skin symptoms as well as for other categories, with no reference to possible pathophysiological mechanisms, like allergic reaction, for which there seems no justification most of the time.
The use of strict case definitions assures homogeneous diagnostic groups with possibility of epidemiological studies for risk factors and sequelae. Together with follow up this may lead to founded adjustment of indications, contraindications, vaccines or schedules as well as to proper precautions when administering a next dose. For collapse reactions this kind of follow up study has shown a low rate of recurrence after further pertussis vaccinations [40,64]. See also under specific events paragraph 7.3. In a substantial share of the reports the event specifics and subsequent diagnosis and causality assessments undergo significant adjustments after validation and additional information has been received. Categorisation is done according to criteria for diagnosis and case definitions and for causality. For the aggregated analysis all cases have been re-appraised.

7.1.3 Reporters

The vast majority of notifications come from Child Health Clinic staff. As professional standards require asking after adverse events routinely and nearly all children attend the clinics this gives good coverage of the safety surveillance. It is expected that few severe events be missed. We try to stress in training courses of paediatricians and child neurologists that they also should report more often. Especially (severe) events or diseases after vaccinations, which they themselves hold to be (clearly) coincidental but parents may regard as vaccine-associated (later on). This is not to much avail apparently since the number of reports by paediatricians remains very low. We have studied two specific adverse events (i.e. ITP and ataxia following MMR or any other vaccine) through the NSCK (the Netherlands Paediatricians Surveillance Unit). Adverse events occurring in a predefined risk window are included in this annual report. This accounts for both the increase of reports of paediatricians and a substantial part of the increase in (e-) mail reports in 2003.
It is important even if paediatricians are not the initial reporters that hospital information is made readily available when Clinic staff report the event. Only then is it possible to

counteract public unrest (pro-actively). This should also enhance the ability of the safety surveillance system to detect new and hitherto unknown adverse events. Reporting by paediatricians or GP's may lead to earlier notifications. It does not make contact with the Child Health Clinics unnecessary however, as the latter have valuable information on growth, development and health and of course data on the administered vaccines. Therefore we have asked Clinic personnel to notify anyway, regardless of (supposed) reporting by others. This includes cases where they asked parents to report themselves or heard from the parents that they have done so. Distribution over the different reporting sources has remained stable over the years however, except for some absolute and relative increase in reporting by parents. The number of reports primarily by parents has gone up steadily over the years but has stabilised now. This is may be a sign of increased assertiveness of parents but in a large proportion of cases parents are advised to report themselves by the clinic staff.
Parents do however more often than before contact us spontaneously after notification by the clinic. The Programme information service at the RIVM is significantly more contacted by the public in the last years either for information or because of apprehension about the safety of the vaccination programme.
Events that are more easily missed in the reports are those following vaccinations without a close follow up Clinic visit. This will possibly affect MMR1 vaccinations to some extent and especially the revaccinations at four and nine years of age. The current economising by the government in the Child Health Care in the 1-4 year olds with less Clinic visits and fewer minutes available per child is feared to have an adverse effect of vaccine safety surveillance especially of MMR1 and MenC vaccinations. Clinic staff signals increasingly that they just do not have time anymore to report. In the information leaflets for the parents it should be stated more explicitly that in case of severe or peculiar unexpected adverse events, parents should not only contact the GP but (later) also the clinic. Active follow up as started in the end of 2003, which received some financial support from the EU (European research programme for improved vaccine safety surveillance-EUsafevac), should throw some light on the extent of underreporting of some specific adverse events following DPTP-Hib. See also subparagraphs 7.1.6. and 7.2.1.

7.1.4 Source of Information

Additional information about the adverse event was retrieved from others than the initial reporter in 82% (72%, 78% and 67% in 2002, 2001 and 2000). This large proportion reflects both the increased apprehension in professionals and parents and the incompleteness of the information of the initial report. See also what is said about this under verification and assessment in subparagraph 7.1.2. Parents were quite often reporters of AEFI (8.2%) and they were contacted (actively or spontaneously) for further specific information in another 75% of cases. Parents do call the telephone service for professionals for information about the (safety of the) programme, increasingly. Anti-vaccine-movements add substantially to public concern about possible adverse events in the Netherlands as in other countries [76]. Contact with parents is often necessary anyway since permission has to be acquired to request medical information from GP or hospital. More often than not the reporters have insufficient

information, necessary for definite categorisation and causality assessment. Often the reporters do not have first hand information. Hospital information was received in 24% of cases (327) with still a deficit of around 50 in which the paediatrician examined the child but we did not receive information despite repeated request and permission by the parents. In the end most of these cases could be assessed reliably however.

7.1.5 Regional Distribution and Reporting Rates

We have standardised the number of reports per region on rate per 1000 vaccinated infants (for the first three doses DPTP/Hib). Since the actual numbers of vaccination coverage and population in the different regions are only available up till 2000 as yet, the rates for 2001, 2002 and 2003 are based on these data. Apart from the smaller birth cohort (± 4% less since 2000, according to PEA and CBS data [53,56]) this is held to have little distorting influence. The overall reporting rate has gone up significantly in 2001 with stabilisation in 2002. The increase in 2003 is consistent with the introduction of the menC and the influx of actively reported cases through the NSCK. Regional reporting rates are consistent with those in 2002. There was a little less dispersion in the overall regional rates than in 2002. Two regions had significantly higher reporting rate and two lower. If we apply the country average to those regions it would have meant 5-8 extra reports. For major events the difference would be only one report. The overall proportion of major events was significantly lower than in 2002, with 43% major adverse reactions in 2003 opposed to 47% and 49% in 2002 and 2001. Trends in reporting rates may be influenced also by the introduction of two new vaccines in the programme (aK and menC vaccine), and must therefore be interpreted with extra care. See for more details under paragraph 7.2 and 7.3.

7.1.6 Passive Surveillance versus Active surveillance

Active surveillance may supplement our enhanced passive surveillance system. Periodic study of tolerability of the used vaccines is warranted, not only in case of signals or expected change in this respect. In the menC campaign apart from intensified passive surveillance also registration of acute events at the settings as well as monitoring tolerability have been done[77,78]. A planned study for the tolerability of DPTP/Hib got thwarted several times because the planned MenB trial was postponed and in between an accelerated schedule for DPTP/Hib vaccines was adopted. This accelerated schedule however in itself deserves specific study of overall tolerability at a younger age. In 2004 we plan to complete an active study in about a total of 30-40,000 doses DPTP-Hib for rare and more severe events. This study serves also the EUsafevac project in which the Netherlands was a partner. This EUsafevac project (2001-2003) for improved vaccine safety surveillance explored possibilities, feasibilities and shortcomings of different designs of safety studies as supplementation of the regular passive safety surveillance in the different member countries. This active study will increase our knowledge of several more severe adverse events, e.g. persistent screaming, very high fever and discoloured leg syndrome for which incidence rates are not known precisely. These outcomes will also be of use in risk communication to providers and parents (paragraph 7.4). This study may also assess the performance of our

current enhanced passive surveillance system. Passive surveillance however will remain the backbone of post marketing surveillance and the most appropriate tool in signal detecting. For testing hypotheses generated by passive surveillance systems active follow up through monitoring or data linkage designs need to be employed. With relying on only active surveillance the safety-surveillance-system is “unmanned” for testing generated hypotheses since that will not be possible anymore within the same system. Therefore enhanced passive surveillance as well as designs for hypotheses testing are of importance and should be employed in the right order [79].

7.2 Number of Reports

Since the large step up of 1998, the reporting rate has stabilised in 1999 and 2000. In 2001 however, there was another increase (17%) that cannot be explained by the larger birth cohort (plus 2.5%) or a larger number of administered vaccines. In 2002 the numbers have stabilised however with 1332 reports (1331 reports in 2001). In 2003 there was a small increase in reports, to 1374. The capacity of the telephone service, the main route for reporting, has been very much under stress in 2000 and 2001, due to lack of resources with possibly subsequent inaccessibility. Number of reports in 2003 suggests that accessibility has been sufficient and that reports reached RIVM in 2002 despite the burden of the menC campaign. Reporters know of course that notification can also be done by mail. There is only very small increase in reporting by mail, however. The telephone service is also used for consultation and advice and since quite a high number of reports reach us because of the need for consultation, we have to assure that the telephone service is “open”, in order not to miss a substantial part of notifications. There is a small increase in multiple reports: 79 compared to 58 and 65 in 2002 and 2001 (versus 40 in 2000 and 44 in 1999). Minor common events that come up during follow up by RIVM are not included as multiple report unless the events are explicitly reported time spaced. Uncommon and major events are always included in the numbers whichever way the events came to the attention of the surveillance system. This policy has not been changed since 1994. See for criteria the materials en methods section, paragraphs 4 and 5.

The small increase in reports in 2003 can be explained by the new menC vaccination simultaneous with MMR, causing some increased awareness and the influx of active reports through NSCK. There was another increase in the number of compound reports to 26 (compared to 21 in 2002 and 11 in 2001) is mainly because a rise in the number of children with high fever not being considered as part of the event. To some extend criteria for the dividing line between minor and major are arbitrary therefor small fluctuations in numbers may be without meaning. Reporting criteria have not changed either over the years, but awareness of professionals and the public has increased lately, partly because of the publicity around new/to be introduced vaccines. Recently the need for vaccinations and their safety has been questioned by certain groups [13,76]. Public awareness of the seriousness of the target diseases has diminished since the illnesses have been effectively prevented for many years now [80]. Consequently more value is attached to (potential) side effects. This influences the readiness to report perceived adverse reactions. Reporting criteria for adverse events

following immunisation are flexible and subject to personal interpretation and circumstances. Our system registers any notification, regardless the reporting criteria, time interval or causality.

7.2.1 Underreporting

Reducing underreporting is of special importance in passive surveillance systems, especially of selective underreporting. Since 1994 we have put extra effort into this, as has been discussed in previous annual reports [33,34,35,36,38,39,41]. 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 [35]. 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 [36]. The number of reports in 2000 were comparable to 1998, but there was some shift in reports for some age specific adverse events, held to be due to the effect of the new schedule, with earlier start for some age specific adverse events [38]. The increase in number of reported AEFI in 2001 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 [39]. The number of reported events is not evenly distributed over all event categories and over all vaccine doses and has changed somewhat in 2002 compared to 2001. See subparagraphs below and discussion of the specific adverse events in paragraph 7.3.
To get information on incidence rates of some more severe events RIVM has started active surveillance in December 2003 aiming at 30-40,000 doses DKTP-Hib. This will also supply an estimation of the degree of underreporting. This study will be published in 2005.
The stable rather evenly distribution of the reporting rates over the country suggest a satisfactory performance of the passive surveillance.

7.2.2 Distribution over Vaccines and Dose

The distribution (relative frequency) of all reported AEFI over the different (doses of) vaccines is rather similar to 1994-2002 (table 7 and figure 3). This gives no indication of selective underreporting and points to very stable reporting habits. There is a stable number of reports on DPTP/Hib and the change to mixed administration of DPTP-Hib did apparently not result in a change in the number or the nature of reported adverse events. There was some increase in reports concerning MMR, quite consistently with the introduction of menC vaccine simultaneously with also some effect of the active surveillance of ITP through NSCK. Also some late reports concerning the menC campaign were received. The numbers of reports following the 4-year dose or DTP and aK increased somewhat. The reporting patterns over the different months in 2002 and 2003 for simultaneous DPTP and Hib and mixed DPTP-Hib were very similar.

7.2.3 Distribution over Events

The distribution of reports across event categories is also rather similar over the years (table 6 and figure 4). Within each event category over the different (doses of) vaccines some increase/decrease may be random fluctuations. See for specifics the subparagraphs under 7.3. There is no indication of systematic underreporting. The reporting rate of collapse reactions and febrile convulsions have been rather stable and close to incidence rates shown by prospective studies [81,82,83]. However, background rates of most events are not known, and there may be (substantial) underreporting for some. The before mentioned large active surveillance study of 30-40,000 doses DPTP-Hib may supply more insight. The passive reporting rate of ITP following MMR for instance has been lower than some studies suggest [84,85]. We have followed this up in active study design. See under the specific event in paragraph 7.3. Since reporting criteria include severe events regardless of assumed causal relation, perhaps all severe events, occurring in the applicable risk window for the specific event and vaccine, should be reported. The number of reported discoloured legs has been rather stable over the years, with perhaps some step up since the use of higher potency pertussis vaccine and another small step up in 2001. However, we have no indication of the completeness of reporting of this specific event. Therefor discoloured legs are included in the active surveillance that has been supported by the EUsafevac project. Persistent screaming, as we have stipulated before, shows underreporting, in view of estimates in prospective studies (that did not apply uniform case definitions). In some cases, during our assessment of notifications of persistent screaming, verification showed that some reports did not fulfil the agreed current case definition. This case definition is consistent with the one defined by the Brighton Collaboration [69,86]. In 2000 there was a significant increase in reported collapse reactions possibly because of the change in the schedule. For 2001 there was another increase in collapse reactions may be again due to a further decrease in age of vaccination. In 2002 these figures stabilised, underlining the need for investigation of this signal. The decrease in numbers of reported collapse in this report might have several explanations that will have to be studied separately. Some other changes in the numbers of convulsions, general illness will be discussed under the specific event paragraphs under 7.3. See for further information also 7.2.5.

7.2.4 Severity, Reporting Interval, Causality and Level of Intervention

We have checked for the different severity markers/parameters, such as major versus minor events and level of intervention from going back to the Clinic to hospital admission. Those gradings of the events do not go parallel with medical importance. Perception of parents and professionals and impact also plays a role.

Parents contacted the clinic or phoned the GP for 216 events (less than in 2002 with 242 and 2001 with 272) but still more than in the previous years (183, 168 and 94 in 2000, 1998 and 1997), and 657 were actually seen by the GP or hospital specialist (588, 569, 525, 472 and 348 in 2002, 2001, 2000, 1998 and 1997). The relative frequency of parents seeking medical has gone up since 1996 and 1997 from 54% to 66% in 2003. This also seems to point to increased concern if not to increased severity.

The reporting intervals, another indicator of severity or anxiety, for different doses and events have been compared. The reporting interval, did not shorten again, but was again 35% within 4 weeks (before the next clinic visit) the same as in 2002 and 2001, compared to 37.5% in 2000 and to 33.4% in 1998. The reporting interval of MMR was, with reporting within 4 weeks was 40% compared to 44% in 2002 and 47% in 2001 (41% in 2000 and 34% in 1998). For DPTP/Hib vaccinations 31% of events were reported within 4 weeks equal to 2002.
59% of the 222 (131) reported events after MMR were considered adverse reactions in 2003 (60% of 188 in 2002). Absolute numbers of adverse reactions following MMR fluctuated between 104 and 113 in the last five years.
For the first three doses of DPTP/Hib, the percentage considered to be adverse reactions was comparable to former years with 85% (86%, 88% and 84% in 2002, 2001 and 2000). For the fourth dose of DPTP/Hib the percentage of adverse reactions decreased to 73%, compensating for the increase in reports (79%, 76% and 85% in 2002, 2001 and 2000/1998).
The overall percentage of assessed adverse reactions (with causality assessed as certain, probable or possible) is 78% low in the range over the last seven years (78%-84%). This is in part explainable by the diluting effect of the newly introduced mildly reactogenic vaccines, like menC and HepB.
The share of major events, by our definition, together with minor events with hospital admission was a little lower than in former years with 53% and the decrease attributable to the lower number of diagnosed collapse cases and possibly the “dilution” because of less reactogenic vaccines (55%, 58%, 58%, 54% and 56% in 2002, 2001, 2000, 1998 and 1997).

7.2.5 Accelerated Schedule

The change in schedule since the 1999 birth cohort did not affect the reporting rate in 2000. The distribution over the different vaccine doses and events was rather similar to before. The younger age at vaccination for the first three doses did not result in a major shift in total numbers and reported events. Therefor, reported events appear to be more dose- than age-specific. It is known that vaccination at a younger age results in less pronounced fever and less local reactions than at a later age [87]. Since the event categories of minor and major general illness are very heterogeneous, the numbers presented here do not yield firm conclusions. The increase in numbers in 2001 was, apart from collapse, discoloured legs, and persistent screaming, mainly due to pallor and crying in the minor illness group. This could be the effect of better adherence to the accelerated schedule with on average younger age at vaccination reflecting the less stable vasomotor system. The increase of collapse reactions in 2000 and 1999 already pointed in this direction. The stable numbers for the other vaccines and doses is in line with this for these vaccinations are not affected by the new schedule. Since PEA data on vaccination do not include the exact day of vaccination we have no precise data on the timeliness of the first three doses. This warrants further investigation to test this hypothesis. (A feasibility pilot performed in December 2003, in collaboration with the data manager of the PEA on a subgroup of registered children in the northern three provinces supported this hypothesis.) The small decrease in reported collapse reaction in 2003, may in part be explained by some shift to pallor in the general illness category and

some to the atypical attacks but also point to decreasing adherence to the schedule and or lower vaccine coverage, as preliminary data of the PEA also suggest. A small decrease in birth cohort may also have contributed. A special nation wide query in the PEA databases may substantiate or refute this assumption of younger age and uptake. Active follow up, as started for the EUsafevac project may shed light on the incidence rates of some of these age specific events and on the age at vaccination. See under collapse and discoloured legs below.

7.3 Specific Events

In addition to what is said in paragraph 7.1 and 7.2 on specific adverse events with respect to the (shift in) numbers in reported adverse events, some specific events or event categories are discussed below.

7.3.1 Collapse reaction

Reports of collapse reactions appear to have truly increased in 2001 with 21% compared to 2000 but have stabilised again in 2002 (270 versus 268 in 2002 and 2001 respectively). Numbers and distribution over the vaccine doses have been rather stable over the past years, with around 100 reports of collapse following the first DPTP/Hib dose (at three months of age) and approximately 25 and 15 reports after the second and third dose up till 1998. Since the change in schedule the total number of reported collapse reactions has nearly doubled (to 266 in 2002) for the first three doses (OR 1.86, c.i. 1.52-2.27). Distribution again in 2002 over the different doses suggests a strong age effect but also a dose effect since the number of collapse after the first vaccination nearly doubled but after the second vaccination is only half of the number at three months of age before the change in schedule. The number of reported collapse reactions at three months of age, assuming the average age to be the same as earlier with the first dose, would have been about 100 instead of the actually reported 50. For 2003 a little less reports have received, with also al smaller number after the second dose. We have little reason to believe that this is due to reporting bias or more or less underreporting. Apparently, to some extent a previously received dose of DPTP/Hib vaccine protects against collapse reaction at three months of age. Cytokines/mediators/interleukins that are part of the primary immune response but are not formed (as much) following subsequent contacts with the antigens may play a role. We will comment on this in our report on collapse reactions (in preparation). The current decrease 2003 will have to be studied as well. Once collapse reaction occurred after Hib only, showing that collapse reactions are not the primacy of whole cell pertussis vaccines.
There were also some reported recurrent collapses, 10 times, less than in 2002 and 2001 (12 and 18), some with (very) incomplete episodes. The number of recurrences is still higher than in the years before the change in schedule. This may be an indication that the accelerated schedule raises the risk on recurrence a little. We plan to look into this more systematically if resources permit.

7.3.2 Discoloured legs

Numbers of reported discoloured legs are similar to 2002. Some of the above remarks on collapse reactions also apply here. Distribution over the different doses remained the more or less the same, with some effect of the younger age, also suggesting a stronger dose than age effect unless the average age for the second and third dose still lags behind. Lacking incidence rates of discoloured legs from prospective studies, we can only speculate. The reporting rate of the discoloured leg syndrome has been rather constant since we made it a specific category and applied case definitions, until this year, with however some levelling of the numbers for the first three doses since the new schedule applies. The numbers for the fourth dose remain low. This does not suggest selective underreporting. We will try to estimate incidence rates in the active follow up started under the EUsafevac project. Whether there is some overlap with subcategories under local reactions and skin manifestations will be looked into. The newly reported syndrome of swollen limp or extensive limp swelling (ELS, mainly after subsequent doses of aK vaccine in other countries) seems to be reported in the Netherlands also a few times. Because of lack of uniform case definitions these reports may be in all three categories. We will look for consensus in the Brighton collaboration for this event and (re) apply a consistent case definition later on the reported events [88,89].
We plan to report on discoloured legs in a separate publication that will include some follow-up data on subsequent vaccinations if resources permit. An interesting feature is that the proportion double-sided discoloured legs remained very high even now that usually only one injection is administered since the change to mix DPTP-Hib.
The number of compound reports with both collapse reaction and discoloured legs was nine, a little less than the12 cases in 2002 (6, 6, 7, 8, 7 and 8 in 1996, 1997, 1998, 1999, 2000 and 2001). Whether the accelerated schedule increases the risk of recurrence of the discoloured legs or not remains to be seen. Recurrence does happen, not necessarily following the next dose, but remains without sequelae. 17 recurrences were reported in 2003, three times not considered causally related (12 in 2002). This will be looked into if resources permit.

7.3.3 Apnoea

Five children with apnoea or decrease in oxygenation were reported in 2003. Four of these children were pre-term infants. Twice the event was considered unrelated however. Only one apnoea was reported in 2002. In 2001 we have not been notified of apnoea even once. In 1999 and 2000 we had several reports of apnoeaic incidents in (extremely) premature children. This is apart from the apnoea in possible BHS or as part of convulsions or collapse reactions.
Risk benefit balance of the vaccination in extremely premature children favours vaccination at an early age. Pertussis is extremely hazardous to them. Therefore the normal accelerated schedule may be applied for premature children. There is a (increasing?) tendency to vaccinate those very premature infants during the (primary) hospitalisation. Since this does not prevent the event to happen we feel that perhaps we should have received more notifications.

7.3.4 Convulsions and Atypical Attacks

The number of (classic) febrile convulsions following DPTP/Hib and MMR1 vaccinations were rather similar to 2002, 2001, 2000, 1999 and 1998. This is not surprising since these events occur most frequently after the fourth dose, and this dose is not affected by the change in schedule. In 2003 three febrile convulsions after the third (2) and second (1) dose of DPTP/Hib were reported. This may reflect the younger age of this dose on average, with subsequent lower (background) rate of febrile convulsions. The number of reported atypical attacks was a little higher than in 2002. Since this subcategory is the dustbin for not easily classifiable paroxysmal events fluctuation in the numbers is not surprising. We follow the reports in this subgroup with scrutiny but up till now no specific trends or signals have come up. The numbers is this subgroup are (very much) dependent to 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. The stable and low number of reports of non-febrile convulsions may reflect non-causality in the first place [83]. Since 1996 numbers vary between 0-6 reports a year.

7.3.5 Local Reactions and Abscess

The number of reported abscesses has stabilised, with six reports in 2003. As in previous years, no faulty procedures were detected. In the future, we will look into risk factors, like eczema and possibly parents working in health care.

7.3.6 Skin Symptoms and Allergy

Up till 2001 the number of reported skin symptoms remained remarkably stable over the years, with a similar distribution over vaccines and type of efflorescence. In 2002 there was an increase however with levelling in 2003. This may have been influenced by the introduction of two new vaccines, which may cause increased awareness and apprehension about (allergic) reactions. None of the reported cases were considered to be allergic reaction to the vaccines. With the change in schedule, we expect that more often than before signs of eczema in prone children will follow vaccination. This is not because the vaccine causes eczema but because of the natural history of atopic disease with appearance of symptoms at 2-3 months of age and the shift of the first vaccine from three to two months of age. The numbers do show some increased reporting however reflecting increased apprehension of vaccination causing allergic disease. Several literature reviews have looked into this. There appears to be no scientific support for this hypothesis [74,90,91,92,93].

7.3.7 ITP, Gait disturbance (ataxia)

ITP numbers have remained low throughout the years. An active surveillance study has been started in 2002 through the Netherlands Paediatric Surveillance Unit (NSCK) in order to gain more insight on ITP and its relation to vaccinations [37,85,94,95]. We will report on the active surveillance through NSCK separately in the first half of 2005.
In the year under report numbers have increased with four spontaneous reports, once later also through NSCK, with another 21 only through the NSCK study. 11 Times causality was

considered possible, all in children receiving MMR. 14 Reported ITP were considered coincidentel events with the causal relation of ITP following other RVP vaccines remaining speculative. We conclude so far that this is better reporting and not true increase in adverse reactions. A seasonal influence is plausible also, since the rate is higher than in 2002, when the NSCK study was in place as well.
Biologically, it is also plausible that MMR may cause ataxia, but there are no systematic data [96]. We get very few reports, maybe because it is a rare disorder and because of the lack of causal relation with the vaccine. In the year under report several cases of limping, increased falling have been reported. Only three children fulfilled criteria for ataxia. Twice the event followed MMR1 but once outside the risk window. The first symptoms were 1 day after the MMR vaccination and nearly two weeks after an airway infection. She recovered after one week. Ataxia has also been included in the active surveillance study through NSCK; one report has been received, considered a chance occurrence.

7.3.8 Anaphylactic shock

Most feared of all adverse reactions may be anaphylactic shock. We never had a report of anaphylactic shock caused by the current vaccines of RVP. After so many doses, apparently it does not occur with these vaccines. The practice advocated by IGZ of vaccinating all children in Child Health Clinic settings or mass vaccination at school age seems wise and the non-availability of emergency sets seems justified. There was one nine year old suspected of anaphylaxis, but this appeared to be syncope with myoclonic jerks, repeatedly. The child was eventually presented in hospital and admitted for a night. There it was diagnosed as vasovagal episode. Similar episodes occurred before when blood was drawn. This event has been categorised under faints.

7.3.9 Encephalopathy

Encephalopathy following pertussis vaccination seems to be one of the “wrecks of once known and acknowledged truths strewn on the pathway of medicine” (citation of Barbara Tuchman). Since 1987 we have had no report of encephalopathy possibly attributable to DPTP (pertussis) vaccination. All reported events had other aetiology, like chromosomal or genetic disorders, like Reye syndrome, virus or mycoplasma encephalitis, metabolic diseases or intoxication (salicylate or Tramal e.g.). Also some vascular accidents like thrombosis with underlying clotting disorders have come to light. Lately some children with shaken baby syndrome were reported. The increased possibilities to detect metabolic diseases and chromosomal or genetic disorders have greatly contributed to etiological diagnostics in these kind of events, and so have virological tests, PCR and last but not least MRI.
Reports of encephalitis following MMR are rare. In a few instances causal relation could not be ruled out, since no definite cause could be identified and the event occurred in the risk window for MMR (1: 500,000-1,000,000 children). In the year under report, no reports were received of encephalopathy.
Two children with prolonged post-ictal state following complex febrile convulsions 8 days after MMR1 vaccination fully recovered. These events are booked under convulsions. Two

other children, booked under general major illness, suffered (possible) brain infarction. The one child had vasculitis as complication of chickenpox with underlying factor V Leiden deficiency. The other child had transient hemi-paralysis with heriditary proteine S deficiency. Both these events were considered unrelated to the vaccination.

7.3.10 Pervasive Disorders and Retardation

Press allegations about possible causal relation between MMR vaccination and autism dented the confidence of parents in the vaccination programme [91,97]. Despite the fact that based on scientific evidence renowned (groups of) scientists have refuted these alleged associations, especially in the United Kingdom and Ireland the vaccination coverage dropped considerably [98,99]. We have received some reports on behavioural problems in the autistic spectrum, often quite some years after the MMR vaccination. 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 reports of events that have attracted attention in the press 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 [100,101]. In the year under report no pervasive disorders have been reported.

7.3.11 Epilepsy

In 2001 there has been some increase in reports on epilepsy compared to previous years, concerning very small numbers, in 2002 numbers were very low again however as in 2003. All these were considered not related to the vaccination. Numbers may reflect (public) apprehension. 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 [83]. 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 [54,102]. However, the age at which it occurs coincides with the vaccination schedule.

7.3.12 Death

This year three children were reported that died some time after vaccinations under the RVP. This is in line with expectations considering the background rate. In none of these three cases the vaccination was considered to have caused the death. In two children however the vaccination did to some extent play a role indirectly with wrong decisions made by parents or professionals. It is important that parents and professionals are educated in what (not) to expect and how to address this.
Systematic studies and evaluation of the Institute of Medicine have shown infant death to be unrelated to childhood vaccinations [103]. 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 surroundings 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 week to 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. To explain that assessment of the involvement of prior vaccination is done routinely and not only if there is suspected contribution of the vaccination in the death will satisfy most parents.

7.4 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. See also under paragraph 7.1. 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 side effects. 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.

7.4.1 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 [32,33,34,35,36,38,39]. 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.

7.4.2 Contraindications

Contraindications for the RVP vaccines have been abandoned more or less completely [41,43,45,104,105]. 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. In the year under report abandoned contraindications do not seem to have contributed much to the number of reported events. And therefore prevention of side effects will not gain much in using more strict contraindications and only result in a loss of protection.

7.4.3 Risk Communication

In our telephone information service and in our adverse event surveillance system we are (made) 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 and adequate and up to date information and need 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.rijksvaccinatieprogramma.nl.

7.4.4 Causality Assessment

Causality assessment is important for surveillance purposes of the vaccines, the vaccination programme and for the individuals concerned [41,42]. Individual continuation of the schedule depends on proper assessment. It is important for the entire population served also, as inquietude 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.

7.5 Considerations for the Safety Surveillance of the RVP

Consolidation of the current good reporting practices of clinic staff, with continuous education, also of GP's and paediatricians, is an important aspect of a well performing vaccination programme. In the Netherlands the low threshold telephone service for reporting, consultation and advice has great value for the current enhanced passive surveillance system. The quality of data generated by this system allows systematic follow up and study of specific adverse events. Adjustment of contra-indications and precautions may follow. Detailed trend analysis of specific adverse events, schedules and vaccines or lots is impossible without a robust database system.

The tolerability of the currently used vaccines might be measured, partly in the phase II and III trials in which the registered vaccines are used in the control groups. But in case of changes in schedule or of included already registered vaccines active tolerability monitoring should be included in comparative design (pro-actively thus) [79]. This can not be left to the (different) involved manufacturers but should be a standard part of programme surveillance. Standardised case definitions and reporting criteria are a must [68].

Passive surveillance and active studies are both needed since hypothesis testing cannot ever be done within the same data (system) that generated the hypothesis.

Active surveillance to check on overall tolerability of known but more rare events following the vaccinations has been started under the EU project (EUsafevac, to explore feasibility and constraints); the outcome of this active study with scientific data on incidence rates among others is of direct importance for the safety surveillance of the programme. Gait disturbances (ataxia) and ITP after MMR1 are also studied events in active design through NSCK. These studies may shed light on ITP and gait disturbances as adverse events. All these data may qualify the relative performance of the current enhanced passive surveillance system.

A well performing, good quality passive safety surveillance system such as exists in the Netherlands should not be taken for granted but requires maintenance and investment. On the other hand shortcomings as overdue 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. 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.

After successful prevention of the target diseases the relative weight of adverse events increases. Parents and providers expect careful safety monitoring of the vaccinations. Anti-vaccine-movements will be more active in the future. A comprehensive surveillance system will be instrumental in refuting unfounded allegations.

Providers must be supplied with timely and adequately referenced information about any suggested association of severe adverse events and vaccination in the media or medical press. This will enable them to answer questions from the public. Clinic staff stresses that convincing parents of the benefits of the vaccination programme takes more time than before

and indicates that resources fail. Often parents already have information from other sources and it is not easy, if at all possible, for them to decide on its quality. The sites of anti-vaccine movements on the Internet are much more readily accessible than the more balanced information about the merits of the programme. There is increasingly need for fact sheets per target disease and per vaccine. The possibility of adverse events in general and how to act as parents in case of should be addressed. Periodic actualisation of the RVP guideline book is also necessary but these updates will lag behind and not meet the need for timely information to inform on or refute false allegations. Lately the Minister of Health has recognised this need in a letter about the RVP to the parliament (2nd of October 2000) and repeatedly in answering questions of members of parliament. The start of the project for improving public information on the vaccination programme in 2003, with the launching of a web site is a first step in meeting some of the above discussed needs. Intensified study of specific adverse events through different designs should also be addressed systematically, with follow up of signals detected. Timely allocation of funds is needed with long term commitment.

8 Conclusions and Recommendations

In 2003 the number of reported events increased slightly due to introduction of menC vaccine in the programme, some more multiple reports and influx of some active reports from an NSCK study. This being so accentuates the need to study the explanatory factors for the rather unexpected increase in 2001. The use of the higher potency whole cell pertussis vaccine has caused an increase in reports. The change in schedule in 1999 has not led to an overall increase in reports initially. There was however an increase in reported collapse reactions, which have nevertheless continued in 2001 with an increase in reported discoloured legs, and other symptoms believed to be young-age specific. This has led to an overall increase in the number of reports of 17% and to 21% increase in those specific events. This may be an indication that the earlier start of the vaccination schedule plays a role in these events and might be related to better adherence to the new schedule in 2001. This warrants further investigation, as does the possible rise in number of recurrent collapse reactions. The small decrease in reported collapse in 2003 will have to be studied also since this could well be the result of a tendency to postpone vaccination or even decreased coverage.

Periodically the overall tolerability of vaccines used in the vaccination programme should be studied with special attention to perceptions of providers and parents. The change in schedule from birth cohort 1999 onwards to an earlier start of the programme makes direct comparison with prior studies not entirely possible anymore, however. In addition the change to mixed administration of DPTP-Hib, from March 2003 onwards, may compromise this even more. The study started under the EUsafevac project may supply some information on the tolerability of the vaccine, as may the planned field trials of new vaccines (combinations).

Overall regional distribution of reports seems very satisfactory, although there seems to be substantial underreporting of some adverse events. We have included ITP and gait disturbances (ataxia) following (MMR) vaccination in one of our data linkage pilots (partly funded by EUsafevac project). Detailed study of epidemiology, sequelae, follow up and risk factors should be performed about some specific adverse events, e.g. collapse, discoloured legs and atypical attacks/non-febrile convulsions in the near future. Also we will have to look into the abscess cases for risk factors.

The telephone service for reporting, consultation and advice is an efficient and important tool of the enhanced passive safety surveillance system and in the management of the RVP. Its quality should be maintained and if possible its performance studied.

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 [106,107].

Only then will it 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. 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:

- implementation of a robust database system;
- accelerated annual report on 2004;
- maintenance and evaluation of the current passive surveillance system;
- report on descriptive epidemiology of discoloured legs and follow up also with regard to the accelerated schedule and rate of recurrence;
- belated report on descriptive epidemiology of collapse reactions and follow up, also including the effect of the accelerated schedule;
- further 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 vaccinations, also in relation to the accelerated schedule with start of the programme at a younger age;
- 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 1374 reports must be seen in relation to a total of over 1.5 million vaccines 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 2003

STAATSTOEZICHT OP DE VOLKSGEZONDHEID

INSPECTIE VOOR DE GEZONDHEIDSZORG

Rijksvaccinatieprogramma 2003

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

- 2003: DKTP + Hib + HB[1]
- 2002: DKTP + Hib + HB[1] + BMR + Men C
- 1999: DTP + aK
- 1994: DTP + BMR

1 Algemeen

1.1 Organisatie

De uitvoering van het Rijksvaccinatieprogramma wordt verzorgd door Thuiszorgorganisaties en GGD, 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), voortgekomen uit SVM en sector vaccins van het RIVM, afgeleverd aan de Entadministraties. De distributie en het gebruik van de vaccins geschieden onder administratief 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 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 Financiering

De kosten van de uitvoering van het Rijksvaccinatieprogramma komen ten laste van de in de AWBZ geregelde verzekering. 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.

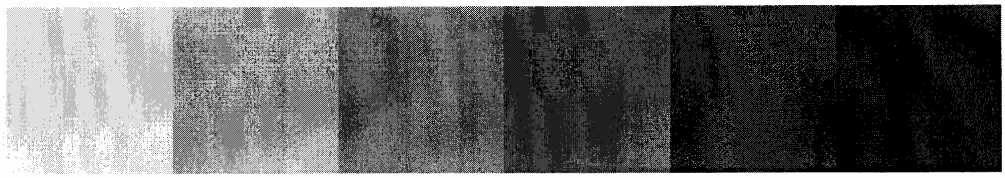
Voor vaccinaties in het kader van het Rijksvaccinatieprogramma door de Thuiszorg of GGD behoeven de ouders geen bijdrage te betalen. Indien ouders kiezen voor een ander vaccin dan dat door de Minister voor gebruik in het RVP is aangewezen en/of indien ouders kiezen voor toediening van RVP-vaccins buiten de leeftijdsmarges die in de AWBZ-verstrekking zijn aangegeven, vervalt het recht op verstrekking en dienen zij zich met hun wensen tot de huisarts te wenden. 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 6) geldt derhalve, dat hiertoe altijd door een arts een indicatie moet zijn gesteld.

1.5

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.
Dit geldt uitsluitend voor de DKTP-, DTP- en BMR-vaccinaties.
In het kader van het Rijksvaccinatieprogramma geldt:

- voor de Hib-vaccinaties dat alleen kinderen voor vaccinatie in aanmerking komen die geboren zijn vanaf 1 april 1993;
- voor de aK-vaccinatie dat alleen kinderen voor vaccinatie in aanmerking komen die geboren zijn vanaf 1 januari 1998 en die de basisserie DKTP hebben voltooid;
- voor de Meningokokken C-vaccinatie dat alleen kinderen voor vaccinatie in aanmerking komen die geboren zijn vanaf 1 juli 2001;
- voor de Hepatitis B-vaccinatie dat alleen kinderen voor vaccinatie in aanmerking komen 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 (prevalentie van dragerschap ≥2%).

[1] Alleen voor de in deze brochure in 2 omschreven doelgroep.



1.6
Voor vaccinaties, gegeven overeenkomstig bovengenoemd Rijksvaccinatieprogramma, doch zonder tussenkomst van de Entadministraties, worden **géén** gratis vaccins ter beschikking gesteld, noch enige vergoeding gegeven.

1.7
Alle nadere regelingen welke met betrekking tot het Rijksvaccinatieprogramma 2003 worden getroffen, vereisen de goedkeuring van de Inspecteur-Generaal voor de Gezondheidszorg.

1.8
Exemplaren van deze folder kunnen worden aangevraagd bij de Inspectie voor de Gezondheidszorg, Postbus 16119, 2500 BC Den Haag, telefoon 070-340 5536.

2 Zuigelingen en kleuters

Vaccinatieschema

- **DKTP** (Difterie - Kinkhoest - Tetanus - Poliomyelitis)

Op de leeftijd van respectievelijk **2, 3** en **4** maanden wordt één DKTP-vaccinatie gegeven.
Er dient minimaal een periode van 4 weken in acht te worden genomen tussen de drie opeenvolgende vaccinaties. De vierde DKTP-vaccinatie wordt bij voorkeur gegeven op de leeftijd van tenminste 11 maanden. Er dient **tenminste een tussenperiode van 6 maanden** in acht te worden genomen tussen de derde DKTP-vaccinatie en de vierde DKTP-vaccinatie.
Dosering: 1 ml INTRAMUSCULAIR.

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

NB Er is toestemming gevraagd aan het College ter Beoordeling van Geneesmiddelen (CBG) om DKTP- en Hib-vaccin te mogen mengen en in één spuit tegelijk toe te dienen. Bij het ter perse gaan van deze brochure was deze toestemming nog niet verleend; u ontvangt hierover separaat bericht. Tot die tijd dient conform het genoemde onder DKTP en Hib gehandeld te worden.

Indien de kinkhoestvaccinatie gecontra-indiceerd is (zie Rudy Burgmeijer & Nico Bolscher 'Vaccinaties bij kinderen', vierde, geheel herziene druk, Koninklijke Van Gorcum 2002) en DTP in plaats van DKTP wordt gegeven, dient degene die de vaccinatie verricht dit **duidelijk** te vermelden en de barcode onleesbaar te maken op de oproepkaart die naar de Entadministratie wordt gezonden. Er zijn overigens geen absolute contra-indicaties tegen de kinkhoestvaccinatie meer.

- **Hib** (Haemophilus influenzae type b)

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

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

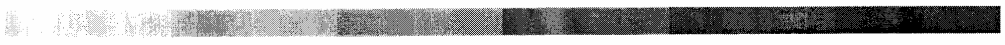
NB Zie het gestelde onder DKTP.

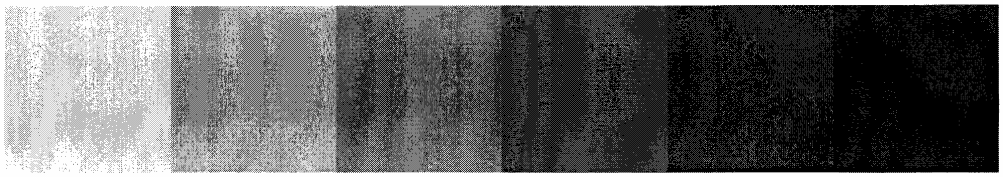
- **HB** (Hepatitis B)

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

NB De HB-vaccinatie van kinderen van HbsAg-positieve moeders (draagsters van het Hepatitis B virus) zal ook in het RVP opgenomen gaan worden. Deze kinderen zullen dan op bovengenoemde wijze, dus met hetzelfde vaccin en op dezelfde tijdstippen, gevaccineerd gaan worden. Advies van de Gezondheidsraad hierover wordt nog afgewacht. U zult hierover nog separaat bericht ontvangen.

[2] De WHO geeft een lijst van landen waar Hepatitis B laag endemisch is (prevalentie van dragerschap < 2%), de zogenaamde negatieve landenlijst: Andorra, Australie, 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, Tsjechie, Uruguay, IJsland, Verenigd Koninkrijk, Verenigde Staten, Zweden en Zwitserland.





- **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.

- **DTP** (Difterie - Tetanus - Poliomyelitis)
De in 1999 geboren kinderen worden in 2003 gerevaccineerd met DTP-vaccin.
Dosering: 1 ml INTRAMUSCULAIR.

- **aK** (Kinkhoest – acellulair vaccin)
De in 1999 geboren kinderen worden in 2003 gerevaccineerd met aK-vaccin, maar uitsluitend indien zij al eerder een volledige serie DKTP-vaccinaties hebben ontvangen.
Er wordt één vaccinatie gegeven. Indien kinderen geen (volledige) serie DKTP-vaccinaties hebben ontvangen, dient deze serie gegeven dan wel afgemaakt te worden.
Dosering: 0,5 ml INTRAMUSCULAIR (in de bovenarm).

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.

Let op

Halvering van de dosering van een vaccin is niet toegestaan. Het effect hiervan op de werkzaamheid is n.l. onbekend, terwijl het niet leidt tot minder bijwerkingen. Ook andere afwijkende doseringen of verdunningen van de vaccins zijn niet toegestaan.

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

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

3 Schoolkinderen

Vaccinatieschema

De in 1994 geboren kinderen worden in 2003 gerevaccineerd met DTP-vaccin. Afhankelijk van de reeds vroeger gegeven vaccinaties worden 1, 2 of 3 vaccinaties gegeven.
Dosering: 1 ml INTRAMUSCULAIR.

De in 1994 geboren kinderen krijgen in 2003 een BMR-vaccinatie.
Dosering: 0,5 ml SUBCUTAAN.

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

4 Simultane vaccinaties en registratie van partijnummers

Simultane vaccinaties dienen altijd in verschillende ledematen te worden toegediend.

Indien deze vaccinaties om een of andere reden niet simultaan kunnen worden gegeven, dient men tussen de vaccinaties de volgende intervallen aan te houden:
- na een D(K)TP-vaccinatie, een Hib-vaccinatie, een HB-vaccinatie, een Men C-vaccinatie en/of een aK-vaccinatie dient men 2 weken te wachten alvorens een ander vaccin mag worden toegediend,
- na een BMR-vaccinatie dient men 4 weken te wachten alvorens een ander vaccin mag worden toegediend.

Er dient per gevaccineerde zuigeling, kleuter en schoolkind bekend te zijn in welke ledematen de DKTP-, Hib-, HB-, Men C-, BMR-, DTP- of aK-vaccinaties zijn toegediend, in verband met de herkenning van (mogelijke) locale bijwerkingen. Daarnaast dienen ook de partijnummers geregistreerd te worden.

5 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 (telefoon 030 274 2424; fax 030 274 4430; Email libris@rivm.nl).

6 Vaccinatieschema per kind

Leeftijd		*Vaccinaties*
2	maanden	DKTP-1 + Hib-1 + HB[3]
3	maanden	DKTP-2 + Hib-2
4	maanden	DKTP-3 + Hib-3 + HB[3]
11(-12)	maanden	DKTP-4 + Hib-4 + HB[3]
14	maanden	BMR-1 + Men C
4	jaar	DTP-5 + aK
9	jaar	DTP-6 + BMR-2

7 Entadministraties

De Entadministratie wordt in het gehele land op geautomatiseerde wijze gevoerd. Voor inlichtingen met betrekking tot het Rijksvaccinatieprogramma en over de wijze van uitvoering kan men zich wenden tot de betreffende Entadministraties.

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
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Postbus 654, 2700 AR Zoetermeer
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Fax 079-331 5047
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Telefoon 010-433 9517
Fax 010-433 9652
Email vandemerwes@ggd.rotterdam.nl

Zeeland
Postbus 53, 4460 AB Goes
Telefoon 0113-224 080
Fax 0113-224 055
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Noord-Brabant
Postbus 8220, 5004 GD Tilburg
Telefoon 013-540 0688
Fax 013-540 0086
Email marionsteeghs@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 030-244 6412
Fax 030-242 0874
Email pdehoogh@entadministraties.nl

Rijksvaccinatieprogramma 2003 tegen:
Difterie, Kinkhoest, Tetanus, Poliomyelitis, Bof, Mazelen, Rodehond, Haemophilus influenzae type b, Meningokokken C en Hepatitis B, voor de kinderen geboren in:
- 2003: DKTP + Hib + HB[3]
- 2002: DKTP + Hib + HB[3] + BMR + Men C
- 1999: DTP + aK
- 1994: DTP + BMR

Prof. dr. J.H. Kingma
Inspecteur-Generaal voor de Gezondheidszorg

Den Haag, december 2002

[3] Alleen voor de in deze brochure in 2 omschreven doelgroep

Appendix 2 Resume Product Information

Vaccines in RVP	Producer	constituents
DKTP-Hib vaccin Diphtheria, whole cell Pertussis, Tetanus and inactivated Poliomyelitis vaccine mixed with Hib-PRP-T vaccine 1 ml	NVI RVG 27930	Diphtheria-toxoid * ≥60 IE Pertussis vaccine 4 IE Tetanus Toxoid* ≥ 60 IE Inactivated poliovirus type 1 40 DE Inactivated poliovirus type 2 4 DE Inactivated poliovirus type 3 7.5 DE Hib-PRP-T equivalent polysaccharide 10µg *adsorbed to aluminium phosphate 1,5 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