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Adverse Events Following Immunisation under the National Vaccination Programme of the Netherlands
Number XI - Reports in 2004

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Het rapport in het kort

Postvaccinale gebeurtenissen na vaccinaties van het Rijksvaccinatieprogramma
Deel XI- Meldingen in 2004

De bijwerkingenbewaking van het Rijksvaccinatieprogramma over 2004 liet een duidelijke toename zien van het aantal meldingen met 56%. Deze toename betrof vooral de mildere en heftiger gewone bekende bijwerkingen als huilen en koorts. De toename in het aantal meldingen is toe te schrijven aan de onrust in de media over de veiligheid van de vaccinaties. Er zijn echter geen nieuwe, onverwachte of ernstige bijwerkingen aan het licht gekomen. In 2004 zijn in het totaal 2141 meldingen ontvangen. Hiervan werd 83% als bijwerking van de vaccinaties beschouwd. Het aantal bijwerkingen moet in relatie worden gezien tot de 1,5 miljoen vaccinaties en de bijna 7 miljoen vaccincomponenten die daarbij worden toegediend. Het Rijksvaccinatieprogramma (RVP) wordt sinds 1962 intensief bewaakt. De meldgraad van vermoede bijwerkingen is hoog met een goede meldbereidheid van de consultatiebureaus. Er is een relatief beperkte onderrapportage. 1765 (83%) van de 2141 meldingen betreffen bijwerkingen. Hierbij ging het in 56% om heftiger verschijnselen, met name hoge koorts, langdurig huilen, collapsreacties en verkleurde benen. Ook koortsstuipen en incidenten met rilligheid, schrikschokken en gespannenheid of juist een hele slappe houding horen hierbij. Hoewel al deze bijwerkingen omstanders erg kunnen laten schrikken zijn ze medisch gezien niet gevaarlijk en laten ze geen restverschijnselen na. Er zijn drie kinderen met hersenontsteking gemeld in 2004, niet veroorzaakt door de vaccinatie maar berustend op andere oorzaken. Bedreigende allergische reacties zijn niet gemeld. 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 vier gemelde overleden kinderen is het overlijden niet door de vaccinaties veroorzaakt.
De gestimuleerde passieve veiligheidsbewaking is een goed en gevoelig instrument om signalen over mogelijke bijwerkingen op te pikken; het systeem laat tevens follow-up onderzoek toe.
Hoewel heftige bijwerkingen na de RVP vaccinaties optreden, zijn ze voorbijgaand en leiden ze niet tot blijvende gevolgen. De grote gezondheidswinst die het RVP oplevert, weegt op tegen de bijwerkingen.

Trefwoorden:
Bijwerking, Rijksvaccinatieprogramma, veiligheidsbewaking, vaccinaties, RVP

Abstract

Adverse Events Following Immunisation under the National Vaccination Programme of the Netherlands
Number XI - Reports in 2004

Adverse events following immunisation (AEFI) in the National Vaccination Programme of the Netherlands (RVP) have been monitored through an enhanced passive surveillance system by RIVM since 1962. From 1984 until 2003 evaluation has been done in close collaboration with the Health Council. An RIVM expert panel continued the reassessment of selected adverse events for 2004. 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 2004 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 2141 AEFI were reported. Of these, 9 (0.4%) were unclassifiable because of insufficient information. In 83% (1765) of the classifiable events a possible causal relation with vaccination was established. These concerned major adverse reactions in 56% and minor adverse reactions in 44% of reports. In 17% (367) of the reports the adverse events were considered chance occurrences. Compared to 2003 there was an increase in number of reports of 56%. This increase was caused by adverse publicity on the safety of the DPTP vaccine. However, this increased attention unveiled no unexpected severe or new adverse events. This adverse publicity started in the first week of 2004 and was immediately picked up by the system. Despite the increase in number of reports the Netherlands Vaccination Programme has a very favourable risk balance.

Keywords:
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
CIb	Centre for Infectious Disease Control
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
MAE	Medical Consultant of PEA
MCADD	Medium Chain ACYL-CoA Dehydrogenase Deficiency
MenC	Meningococcal C infection (vaccine)
MMR	Measles Mumps Rubella vaccine
NSCK	Netherlands Paediatrics Surveillance Unit
NVI	Netherlands Vaccine Institute
PEA	Provincial Immunisation Administration (registry)
PKU	Phenyl Ketonuria
PMS	Post Marketing Surveillance
PRP-T	Polyribosil Ribitol Phosphate Tetanus conjugate vaccine
RIVM	National Institute for Public Health and the Environment

RVP	Netherlands Vaccination Programme
SAE	Serious Adverse Event
TBC	Tuberculosis
WHO	World Health Organisation

Contents

Samenvatting

Vermoede bijwerkingen van vaccinaties van het Rijksvaccinatieprogramma (RVP) worden in Nederland centraal geregistreerd en beoordeeld door het RIVM sinds 1962. De bewaking van de veiligheid van het RVP gebeurde vanaf 1984 tot 2003 in nauwe samenwerking met de Gezondheidsraad (GR). Deze taak is vanaf 2004 overgenomen door een nieuw ingestelde klankbordgroep. De telefonische informatiedienst van het RIVM is een belangrijk instrument in dit passieve bewakingssysteem. In het RIVM jaarrapport zijn alle meldingen ontvangen in het kalenderjaar opgenomen, ongeacht het oorzakelijke verband met de vaccinatie. Dit rapport over 2004 is het elfde jaarrapport.
Van de spontane meldingen kwam 87% telefonisch binnen. Meldingen kwamen merendeels vanuit de Jeugdgezondheidszorg (79%). Nadere gegevens van anderen dan de melder, bijvoorbeeld van ouders, huisarts of ziekenhuis werden in 87% van de meldingen verkregen. Na aanvulling en verificatie werd een (werk) diagnose gesteld met een causaliteitbeoordeling door artsen van het RIVM. Deze beoordeling werd meestal (93%) alleen telefonisch aan de melder teruggerapporteerd. Schriftelijk verslag van geselecteerd, ernstigere gecompliceerde ziektebeelden, werd naar alle medisch betrokkenen gestuurd.
In 2004 zijn 2141 meldingen ontvangen, over 1936 kinderen, op een totaal van meer dan 1,5 miljoen vaccinaties. Negen meldingen (0,4%) waren niet te beoordelen wegens ontbrekende informatie. 1765 Meldingen (83%) werden als bijwerking beoordeeld met mogelijk, waarschijnlijk of zeker causaal verband met de vaccinaties. Een toevallige samenloop werd aangenomen bij 367 (17%) meldingen.
Van de gemelde mildere, zogenaamde “minor” algemene ziekte-, huid- of lokale verschijnselen (939) werd 78% (734) als mogelijke bijwerking geduid. Gemelde zogenoemde “major” postvaccinale gebeurtenissen (1202) werden in 86% (1031) als mogelijke bijwerking beschouwd. Deze “major” verschijnselen betreffen de rubrieken “ziek-major”, stuipen, collaps (flauwtes), verkleurde benen, persistent screaming (≥3 uur aanhoudend krijsen), encefalopathie/-itis (hersenlijden/-ontsteking) en sterfgevallen. Voorts waren er enkele major lokale verschijnselen.
Verkleurde benen (279) hadden op twaalf na een mogelijke causale relatie met de vaccinaties (eenmaal niet te beoordelen).
Collaps, waaronder atypische en onvolledige episodes, werd 318 maal vastgesteld, in veertien gevallen zonder oorzakelijk verband. Daarnaast waren er enkele breath-holding-spells (23), 3 keer zonder oorzakelijk verband, en flauwvallen (37) in oudere kinderen.
Convulsies (98) gingen op acht na gepaard met koorts. Van de convulsies werden er 80 (82%) als mogelijke bijwerking beoordeeld. Van de 104 atypische aanvallen hadden er 77 (75%) een mogelijk causaal verband. Epilepsie (9) werd in geen van de meldingen als bijwerking beoordeeld, maar als coïncidentie.
Persistent screaming (133) werd in 129 gevallen als bijwerking beschouwd.
Koorts van ≥40,5°C was de werkdiagnose bij 123 kinderen uit de “ziek-major”-groep, op 18 na alle beschouwd als mogelijke bijwerking. Van de 71 andere beelden uit de “ziek major” groep was er 14 keer een mogelijk causaal verband. Dit betrof myoclonieën/rillingen (5) en

vaccinitis (4), alle gepaard aan zeer hoge koorts (≥40,5°C). Daarnaast tekort aan bloedplaatjes (ITP, 3) en dehydratie/gastroenteritis (1). Bij de overige 57 meldingen uit de “ziek major”-groep ging het om een toevallige samenloop.
Er waren 14 abcessen. Van 5 abcessen is bekend dat er gekweekt is; 2 waren positief streptokokken groep A, 1 voor pneumokok en 1 voor een anaerobe streptokok.
Er waren nog 11 anderszins heftige lokale reacties. In 2004 zijn 3 kinderen met encefalopathie /-itis gemeld.
De vier sterfgevallen die in 2004 zijn gemeld, zijn alle na uitgebreide evaluatie als coïncidentele gebeurtenis beoordeeld. Drie kinderen hadden een onderliggend lijden, dat het overlijden heeft veroorzaakt. Bij het vierde kind was er een infectie met snel optredend orgaanfalen.
De meeste meldingen (1730) betroffen gelijktijdige vaccinaties tegen difterie, kinkhoest, tetanus, polio (DKTP) en tegen Haemophilus type B infectie (Hib). Bof, mazelen, rodehond (BMR) vaccin was betrokken in 283 van de meldingen, waarvan 254 maal gecombineerd met andere vaccins. In 57% was er een mogelijke causale relatie met de BMR. Dit was 78% voor de andere vaccin(combinatie)s.
Vergeleken met 2003 was er in 2004 een forse stijging in het aantal meldingen. Dit is toe te schrijven aan de onrust over de veiligheid van het gebruikte DKTP-Hib vaccin. Ondanks de grote toename in het aantal meldingen zijn er geen onverwachte, ernstige of nieuwe bijwerkingen aan het licht gekomen.
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). An RIVM expert panel continued the reassessment of selected adverse events for 2004. 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 2004 is the eleventh annual report.
The majority of reports (87%) came in by telephone. Child Health Clinic staff are the main reporters (79%). Parents, GP's and/or hospital provided additional data on request (87%). RIVM made a (working) diagnosis and assessed causality after supplementation and verification of data. The assessment has been communicated to the reporter usually by phone (93%). Written assessments of selected more serious or complicated events, were sent to all medical professionals involved.
In 2004, on a total of over 1.5 million vaccinations, 2141 AEFI were submitted, concerning 1936 children. Of these only 9 (0.4%) were not classifiable because of missing information. Of the classifiable events 1765 (83%) were judged to be possibly, probably or definitely causally related with the vaccination (adverse reactions) and 367 (17%) were considered coincidental events.
So-called "minor" local, skin or systemic events were registered in 939 cases with 734 reports (78%) classified as possible adverse reactions.
The so-called "major" adverse events (grouped under convulsions, collapse, discoloured legs, persistent screaming, major-illness, encephalopathy and death with inclusion of some local reactions) occurred in 1202 cases, in 86% (1031) possible adverse reactions.
Discoloured legs were reported 279 times with possible causal relation in all but twelve.
Collapse, including atypical and incomplete episodes, was diagnosed 318 times, in only 14 cases without causal relation. 23 Breath holding spells were reported, in 3 with inferred causality and 37 times fainting in older children.
Convulsions were diagnosed in 98 cases, in all but 8 with fever. Of the convulsions 80 (82%) were considered causally related. Atypical attack (104) had possible causal relation in 75% (77) of cases. Epilepsy (9) was considered not causally related with the vaccinations in all instances.
129 Reports of persistent screaming (133) were considered adverse reactions.
Fever of $\geq$40.5°C was the working diagnosis in 123 reports of the major-illness group, in all but 18 with inferred causality. Of the other 71 major-illness cases 14 had a possible causal relation. These events were myoclonics/chills (5) and "vaccinitis" (4) all with very high fever ($\geq$40.5^{o}C). Furthermore ITP (3) and dehydration/gastroenteritis (1). The other 57 reported major-illness cases were considered to be unrelated. There were 14 abscesses, with 2 cultures positive for Haemolytic Streptococcus group A, one for Streptococcus Pneumoniae and one

for an anaerobic Streptococcus. Of the nine other abscesses no cultures were taken. Another 11 reported local reactions were considered “major”.
Three cases of encephalopathy /-itis were reported in 2004 and no anaphylactic shock.
In 2004 all four reported deaths were considered chance occurrences after thorough assessment. In three children death was caused by underlying illness. The fourth child had an infection with rapid deterioration and multi-organ failure.
Most frequently (1730) 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 283 times, 254 times with simultaneous other vaccines. In 57% of these reports there was possible causal relation with MMR. For the other vaccine combinations this percentage was 78%.
In 2004 the number of reports increased by 56% compared to 2003. This was caused by the adverse publicity on the safety of the DPTP-Hib vaccine, starting in the first week of 2004. Despite this large increase in number of reported adverse events, no unexpected, severe or new adverse reactions were unveiled.
The total of 2141 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 since 2003. For the reports from 2004 onwards RIVM installed an expert panel.
Since 1994 following the introduction of a vaccine against Haemophilus influenzae type b (Hib) RIVM has reported annually on reported adverse events. These annual reports are based on the year of notification. They include all reported events, irrespective of severity of symptoms or causal relationship with the vaccination. Reported events are ordered by nature and severity of the symptoms and by causal relation. This 2004 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. Starting in the first week of January 2004 numerous reports concerning severe adverse events following DPTP appeared in the public media. In march 2004 the GR advised the Minister of Health to adopt an acellular pertussis containing vaccine as soon as possible [1, 2, 3]. This advice added considerably to the public and political concern about the effectiveness and safety of the RVP. We will pay special attention to the effects of these concerns on reporting of adverse events
This eleventh 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 summarised overview in Dutch over several years 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 [4]. 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). Both safety surveillance and the surveillance of effectiveness are performed by the Department for Infectious Diseases Epidemiology (CIE), independently from vaccine manufacturers[5]. CIE is part of the Centre for Infectious Disease Control (CIb) of RIVM. Requirements for Post Marketing Surveillance of adverse events have been stipulated in Dutch and European guidelines and legislation [6,7]. 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[8]. The WHO keeps a register of adverse reactions as part of the global drug-monitoring programme[9]. Currently there are several international projects to achieve increased quality of safety surveillance and to establish a register specifically for vaccines and vaccination programmes [10,11,12].

Close evaluation of the safety of vaccines is of special importance for maintaining public confidence in the vaccination programme as well as maintaining motivation and confidence of the health care providers. With the successful prevention of the target diseases, the perceived side effects of vaccines gain in importance [13,14]. Not only true side effects but also events with only temporal association with vaccination may jeopardise uptake of the vaccination programme [15]. This has been exemplified in Sweden, in the United Kingdom and in Japan in the seventies and eighties of the last century. Commotion about assumed neurological side effects caused a steep decline in vaccination coverage of pertussis vaccine and resulted in a subsequent rise of pertussis incidence with dozens of deaths and hundreds of children with severe and lasting sequelae of pertussis infection [16]. Also in Eastern Europe the diphtheria epidemics are (mainly) the result of anxiety about safety of vaccination (procedures) [17]. But also recently concerns about safety rather than actual causal associations caused cessation of the hepatitis B programme in France [18,19]. 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 [13,20,21,22,23,24,25,26,27,28]. Subsequent (local) measles epidemics have occurred [29,30,31,32].

To counteract similar (unfounded) disquiet in the past 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 GR has advised the Minister of Health on the safety of the Vaccination Programme with annual reports, up till 2003 (in preparation) [33,34]. For the year under report a RIVM expert panel has taken over the reassessment of selected severe or complex events. For more detailed information see paragraph 5.7. The new website of the RVP increased the possibility of communication with the public about the (safety of the) RVP.

Aggregated analysis of all reported adverse events is published annually by RIVM. Signals may lead to specific follow up and systematic study of selected adverse events. [35,36,37,38,39,40,41,42,43,44,45]. These reports support a better understanding of pathogenesis and risk factors of specific adverse reactions. In turn, this may lead to changes in the vaccine or vaccination procedures or schedules and adjustment of precautions and contra-indications and improved management of adverse events. These reports may also serve for the purpose of public accountability for the safety of the programme [46].

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. For the current schedule see box 1. 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 [47,48]. 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. 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.

From March 1999 onwards the programme starts 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 the third dose at five months of age to all children. It was shown that under the previous schedule about 25% of children had not finished their primary series before six months of age [49]. 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 [50].

Box 1. Schedule of the National Vaccination Programme of the Netherlands in 2004*

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 HepB 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 [51,52]. 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 [53]. 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 replacing the two separate injections. BCG vaccination is not included in the RVP. Vaccination is however offered free of charge to children with higher risk of acquiring tuberculosis when travelling to or staying in countries with a high prevalence. Usually BCG vaccination takes place in the second half-year of life [47]. 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 [47]. 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 Sanofi-Pasteur-MSD (SPMSD) but registered in special presentation form by NVI. aK is produced and registered by GlaxoSmithKline (GSK), with final bulk into vials by NVI. MenC is from Baxter. HepB is produced by SPMSD. SerumStatenInstitute produces BCG. (Summarised product characteristics in 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) [47,54]. The PEA is responsible for further distribution to the providers. It also has the task to implement and monitor cold chain procedures at the Child Health Clinics (CB) and Municipal Health Services (GGD). The Medical Consultant of the PEA (MAE) promotes and guards programme adherence.
The databases of the PEA contain name, sex, address and birth date of all children up till 13 years of age. The databases are linked with the municipal population registers and are updated regularly or on line, for birth, death and migration.
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 neonatal heel prick tests and prenatal screening on infectious diseases, e.g. hepatitis B 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 [48]. Up till four years of age (Pre School) children attend the Child Health Clinic (CB) regularly. At school entry the Municipal Health Service (GGD) takes over. 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, alternately 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 the primary series DPTP/Hib is over 97% and slightly lower for MMR [55,56,57,58]. (Accurate numbers on birth cohort 2002-2004 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 is grounded on a (24-hr) telephone service. Professionals call for consultation and advice on vaccination matters like schedules, contra-indications and precautions and adverse events. In case of adverse events this is taken up as a report. 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 [47]. 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 assumed causality and medical intervention 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 also.

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

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

All notifications are accepted, registered and assessed by RIVM, irrespective of nature and severity of symptoms, diagnoses or time interval. No discrimination is made for 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 are 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 1994, for reasons specified in chapter 2, RIVM publishes annual reports on adverse events.

4 Materials

4.1 Post Vaccination Events

Events following immunisations do not necessarily have causal relation with vaccination. Some have temporal association only and are in fact merely coincidental [13,14,54]. 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) [35,47,59,60].

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 may be 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 (box 2). The same applies 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

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 until 2003. Presently they form the core material for discussion in the RIVM expert panel. For further details see the following paragraphs of this chapter.

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 is a fitting interval and a satisfactory biologic plausibility of vaccine/vaccination as cause of the event in the absence of signs of other causes. 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

Causal relation is considered (highly) *improbable* in case of implausible temporal relation or established other cause of the event. The event is then considered coincidental or chance occurrence. This category includes also events without any causal relation with the

vaccination. If data are insufficient for a (working) diagnosis and causality assessment, the event is listed under *unclassifiable*.
Generally it is evaluated as well, to what extent the vaccine or vaccination has contributed to the event and how. This is especially important if faulty procedures are involved or in case of individual risk factors. 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 is considered a major event.
- General skin symptoms: skin symptoms that are not part of general (rash) illness and not

considered extensions of a local reaction fall in this category. For instance exanthema or other rashes as erythema, urticaria, that are not restricted to the injection site. Circumscriptive 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. Classical breath holding spells with no or very short pallid phase 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 like fever and elevated cell counts in the cerebrospinal fluid.
- Anaphylactic shock: circulatory insufficiency with hypotension and life threatening hypo perfusion 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	major	inconsolable crying for 3 or more hours on end
general skin symptoms	minor	skin symptoms not attributable to systemic disease or local reaction
	major	severe skin symptoms or skin disease
discoloured legs	major	disease entity with diffuse or patchy discoloration of legs not restricted to injection site and/or leg petechiae
faints	major	collapse with pallor or cyanosis, limpness and loss of consciousness; included are also fainting and breath holding spells.
fits	major	seizures with or without fever, epilepsy or atypical attacks that could have been seizures
encephalitis/encephalopathy	major	stupor, coma or abnormal mental status for more than 24 hours not attributable to drugs, intoxication or post-ictal state, with or without markers for cerebral inflammation (age dependent)
anaphylactic shock	major	life threatening circulatory insufficiency in close connection with intake of allergen, with or without laryngeal oedema or bronchospasm.
death	major	any death following vaccination irrespective of cause

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 clinical diagnosis, 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. Coding is done according to strict criteria for case definitions and causality assessment. If there is new follow-up information, the case is reassessed and depending on the information, the original categorisation may be adapted. This applies also for the reassessments done by the expert panel 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 complex cases and may also be used in the discussions 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 and Expert Panel

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. 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 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. The safety surveillance of the RVP is independent from all manufacturers of vaccines as off 2002. This makes the necessity of secondary independent re-assessment by GR less obvious. This coincided with an internal GR realignment of the tasks of this committee, resulting in stopping the individual reassessments.
RIVM has set up an expert panel for the purpose of broad scientific discussion of particular complex adverse events. Currently this group includes specialists on the fields of paediatrics, neurology, immunology, pharmacovigilance and microbiology. Written assessments are reviewed on diagnosis and causality.

5.8 Annual Reports and Aggregated Analysis

The coded forms are used as data sheets for the annual reports. 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 reports over 2001-2003.
For consistent assessment the physicians of RIVM held clinical conferences periodically in which all complex, controversial and otherwise interesting cases are discussed. The coding is performed time spaced and by a different physician from the one that handled the clinical case, in order to reach inherent second opinion and maximum consistency.

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. A copy of these reports to Lareb is sent to the respective vaccine manufacturers. Lareb sends to RIVM all reports received directly from other reporters on programmatically used vaccines.
At the same time RIVM sends annually, or more often when necessary, linelistings of all adverse events (AE) to the vaccine manufacturers that contribute to the National Vaccination Programme.

6 Results

6.1 Number of Reports

In 2004 RIVM received 2141 notifications of adverse events, on a total of nearly 1.4 million vaccination dates with nearly 7 million vaccine components (table 1). These 2141 reports involve 1936 children. 49 Notifications were compound with two (or more) distinct adverse events after one vaccination (date). Eight of these compound reports were also multiple reports, in one child with two compound reports. See paragraph 4.2 for definitions.
132 Notifications were multiple with two (or more) events in one child after different vaccination dates resulting in 280 reports. Multiple and compound reports are listed under the respective event categories. The number of multiple reports increased from 79 in 2000 to 151 in 2003. Compound reports increased also from 24 to 41 in 2000-2003, with an increase from 3-16 multiple-compound reports in the same period. 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. Number and type of reports of notified AEFI in 2000-2004

notifications 2004	children	adverse event reports	reports 2003	2002	2001	2000
single	1756[a]	1756	1166	1174	1178	1036
multiple	132[b]	280	151	111	133	79
compound	40[c]	80	41	34	16	24
compound and multiple	8[d]	25	16	13	4	3
total	1936	2141	1374	1332	1331	1142

[a] 44 children had also reports in previous (26) or following (18) years; these are not included
[b] fourteen children with triple reports and one child with quadruple reports
[c] all children 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 [35,36,37]. In 1998 there was a significant increase in the number of reports judged to be partly due to increased awareness and apprehension, to further reduced underreporting but also to some true increase in actual adverse reactions [38]. In 1999 there was again an increase in number of reports. This was considered 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 [39]. In 2001 there was another increase in the number of reports judged to be possibly due to intensified follow up of the reports both by reporters and by RIVM. Also some better adherence to the accelerated schedule may have played a role, resulting in vaccination on average at a younger age. This might have yielded a

higher number of reports of some more young-age specific events [41,42]. In 2003 implementation of MenC vaccination and HepB vaccine for risk groups may have contributed to some increase in reports.(See reports on 1998 - 2003, 000001004, 000001005, 000001006, 000001007, 000001009 and 240071001 respectively (www.rivm.nl). In the current year the number of reports is much higher than in the three previous years, both for single events and for compound and multiple events. Details will be given in the paragraphs below and inference in the discussion.
The birth cohort has increased gradually up till 2000 from nearly 190,000 in 1996 to over 206,000 in 2000. Since then there is gradual decrease to a little above 194,000 in 2004 [61].

Table 2. Number of reported AEFI per year (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
2004	143	**2141**

[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). We received 178 reports by regular mail, 49 by e-mail (49) and 49 by fax. The percentage written reports fluctuated between 2.3% to 6.2% from 1994 to 2002 with an increase to 7.9% in 2003 and 12,9% in 2004. In 2004 most of the increase in written reports is due to inclusion of some of the RIVM questionnaire reports from an active study started in December 2003 (107). Criteria for inclusion of these questionnaires in this annual report were severity, rarity or extreme (public) concern. See paragraphs 3.4 and 4.2. Questionnaire information obviously has also been included if the event was reported independently by another reporter. Some (14) of the written reports come from an active study of ITP among paediatricians in 2003.

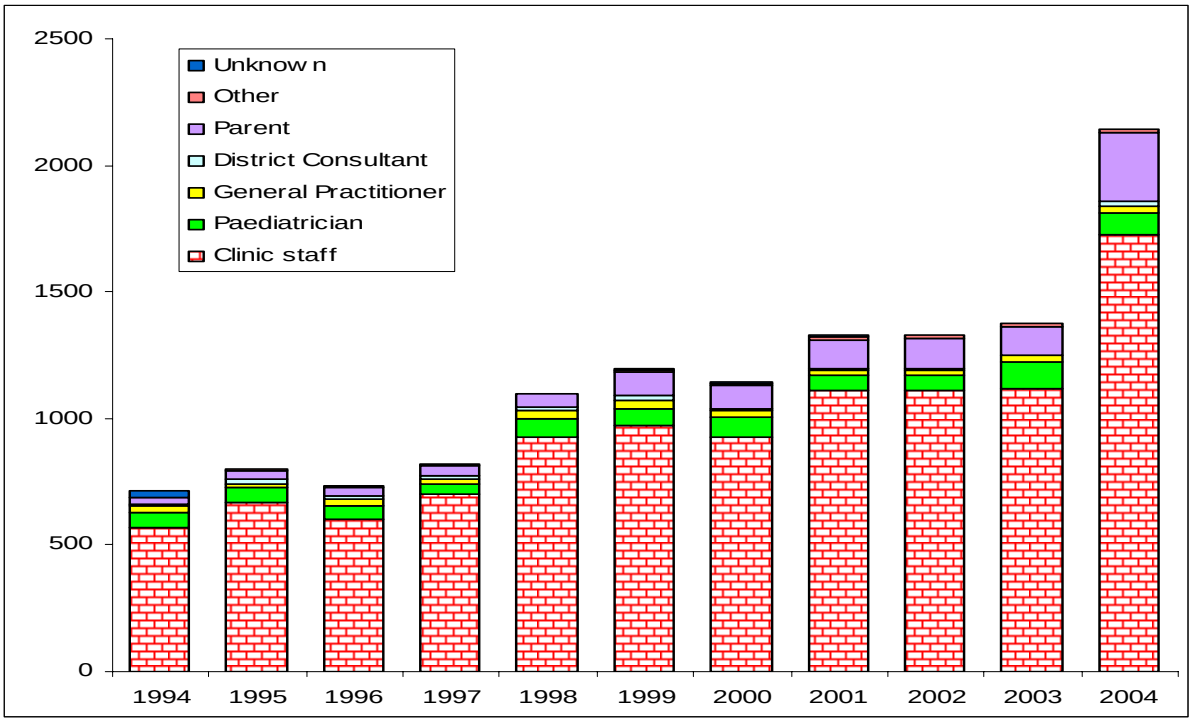


Figure 1. Reporters of adverse events following vaccinations under the RVP

Child Health Clinics accounted for 1685 reports (79%). This percentage varied between 78% and 84% over the years since 1994. Parents of 271 children (12.6%) were the primary reporters, more than in previous years (8.2% in 2003 and 9.1% in 2002). Parents were advised to report directly by clinic staff, but increasingly "find their way in". Additionally we have taken in some reports from the active questionnaire survey on infrequent adverse events after DPTP-Hib vaccination, in which 120 parents were the (primary) reporter. The share of other report sources was more or less stable (detailed information in table 3).

Table 3. Source and reporting route of AEFI in 1994-2004

		1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	*tel*	*mail*[c]
Clinic staff[a]	Physician	474	548	466	547	678	722	687	794	791	741	1199	*1108*	*91*
	Nurse	78	102	116	142	219	221	199	290	282	337	486	*461*	*25*
Paediatrician		60	59	56	39	69	70	80	56	61	108	84	*62*	*22*[d]
General Practitioner		25	13	26	20	35	34	28	18	17	22	24	*23*	*1*
Municipal Health Service		15	18	17	10	31	27	37	31	39	39	44	*39*	*5*
District Consultant		9	18	11	16	15	16	5	11	8	5	21	*17*	*4*
Parent		25	34	35	40	52	91	97	115	121	113	271	*149*	*122e*
Other[b]		5	6	2	7	1	9	7	14	13	9	12	*6*	*6*
Unknown		21	2	3	1	-	7	2	2	-	-	-	-	-
total		712	800	732	822	1100	1197	1142	1331	1332	1374	2141	*1865*	*276*
	(% written)	(4.9)	(3.4)	(3.4)	(6.2)	(2.3)	(3.8)	(3.3)	(3.8)	(4.9)	(7.9)	(12.9)		

[a] including staff of refugee clinics (4)
[b] including reports by Lareb (4), NMS (2), pharmacist (4), dietician (1), councellor(1)
[c] including e-mail (49) and fax (49) reports
[d] including sentinel reports (11)
[e] including questionnaire reports (105)

In 2004 in 13% of the reported events the reporter was the sole informer and information was received from others also in 87%, both spontaneously and requested. This number is higher

than in former years (range 67-82% for 1999-2003). In 93% of the reports the clinics (child health, school health and refugee clinics) supplied information, equal to 2003. Parents were contacted in 90% (1929) 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 higher than in 2003 (83%) and 2002 (76%). Parents were the sole informers in 101 reports of which 50 through the questionnaires. Hospital specialists supplied information in 15.5% of the reports (24% in 2003 and 16% in 2002 and 2001). See for details table 4.

Table 4. Information sources and events of reported AEFI in 2004

																total (%)
info ⇒	clinic*	+	+	+	+	+	+	+	+	-	-	-	-	-	-	1993 (93)
	parent	-	+	+	+	+	-	-	-	+	+	+	-	-	-	1929 (90)
	gen. pract.	-	-	-	+	+	-	+	+	+	-	-	+	-	-	51 (2.4)
	hospital	-	-	+	-	+	+	-	+	-	+	-	-	+	-	332 (15.5)
event ⇓	other	-	-	-	-	-	-	-	-	-	-	-	-	-	+	8 (0.4)
local reaction		15	98	5	2	-	3	-	-	1	-	3	1	1	-	129
general illness	minor	70	519	52	7	2	3	1	-	-	1	41	2	-	6	704
	major	9	108	35	1	4	4	2	-	-	2	15	-	14	-	194
persistent screaming		10	115	3	1	-	-	-	-	-	-	3	-	-	1	133
skin symptoms		14	59	11	3	1	-	1	-	4	2	10	-	1	-	106
discoloured legs		10	220	27	1	-	-	-	-	-	1	19	-	-	1	279
faints		19	278	63	4	1	1	1	-	1	3	6	-	1	-	378
fits		10	107	73	6	-	6	-	2	-	2	4	-	1	-	211
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
encephalopathy/-itis		-	-	-	-	2	1	-	-	-	-	-	-	-	-	3
death		-	-	3	-	-	-	-	-	-	-	-	-	1	-	4
total		157	1504	272	25	10	18	5	2	6	11	101	3	19	8	2141

* 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 many reports this is (preliminarily) achieved in the notifying phone call. In most reports further verification and additional information is necessary for final assessment.

Table 5. Feedback method and events of reported AEFI in 2000-2004

		2000			2001			2002			2003			2004		
event ⇓ feedback method⇒		mail	tel	total	mail	tel	total	mail	tel	total	mail	tel	total	mail	tel	total
local reaction		3	72	75	1	89	90	1	119	120	4	119	123	4	125	129
general illness	minor	8	358	366	21	426	447	12	405	417	16	444	460	16	688	704
	major	18	88	106	14	60	74	20	92	112	51	68	119	33	165	198
persistent screaming		-	39	39	2	47	49	1	45	46	2	53	55	3	130	133
skin symptoms		-	75	75	0	73	73	-	104	104	5	99	104	3	103	106
discoloured legs		5	121	126	14	161	175	4	133	137	9	125	134	15	264	279
faints		17	222	239	34	259	293	20	277	297	35	209	244	25	353	378
fits		15	97	112	22	99	121	16	75	91	47	85	132	37	174	211
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		1	-	1	2	-	2	-	-	-	-	-	-	3	-	3
death		3	-	3	7	-	7	8	-	8	3	0	3	4	-	4
total		70	1072	1142	116	1215	1331	82	1250	1332	172	1202	1374	143	1998	2141

The feedback, both to professionals and parents, is mostly done by telephone. See table 2 in paragraph 6.1 for numbers. 6.7% of reports got a full written assessment in 2004. These were the more complex events or those causing (public) anxiety or extreme uncertainty about subsequent vaccinations. The intention is however to supply a comprehensive written feedback with assessment routinely.

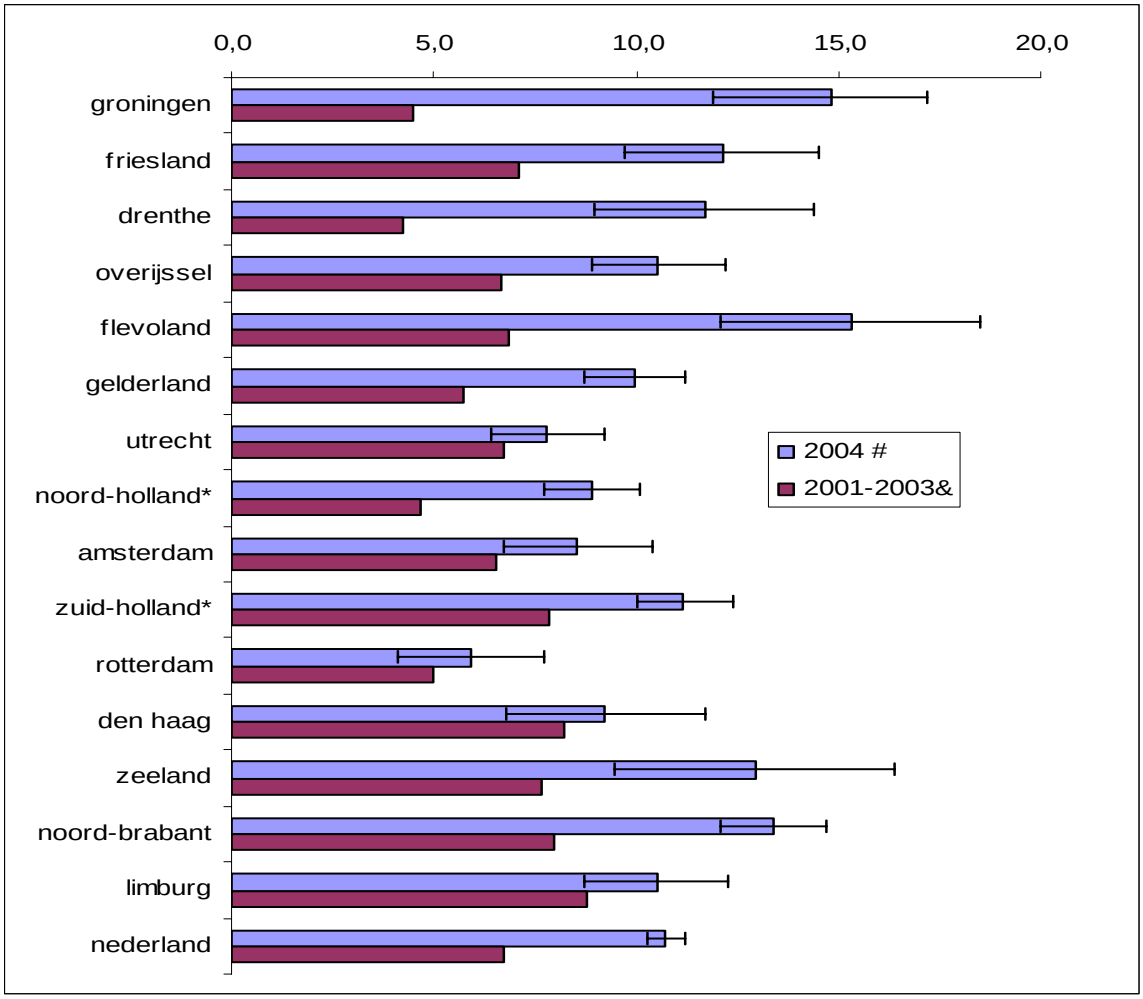
6.3 Regional Distribution

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 mean rates for 2001, 2002 and 2003 and the rate of 2004 were calculated with vaccination coverage data for the 2001. Coverage data on subsequent birth cohorts have not yet been made available [55,56,57,58]. As before we use the coverage data for the first three DPTP doses. 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.
The birth cohort increased from a little below 190,000 in 1996 to 206,619 in 2000. Subsequently the birth cohort decreased yearly to 194,007 in 2004 [61]. Preliminary data from the new centralised vaccination register (Praeventis) indicate that approximately 192,000 of the registered 200,000 children (born between July 2003 and July 2004) received the third DPTP-Hib. Reporting rates for minor and the so-called major events do not show substantial differences between 2001, 2002 and 2003. Therefore we have taken the mean of these numbers. The reporting rate was 10.7 per 1000 vaccinated infants (DPTP-Hib3) in 2004, compared to 6.7 for 2001-2003. For 2004 there was more dispersion of the reporting rates over the different regions (range 5.9–15.3) compared to previous years.

Table 6. Regional distribution of reported AEFI in 2000-2004, per 1000 vaccinated infants[a] with proportionate confidence intervals (major adverse events)

	2000 (major)	2001 (major)	95% c.i. 2001 (major)	2002 (major)	95% c.i. 2002 (major)	2003 (major)	95% c.i. 2003 (major)	2004 (major)	95% c.i. 2004 (major)
Groningen	5.5 (3.7)	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)	14.8 (8.7)	11.9-17.2 (6.5-10.9)
Friesland	5.5 (3.6)	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)	12.1 (7.2)	9.7-14.5 (5.3-9.0)
Drenthe	4.7 (2.5)	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)	11.7 (9.4)	9.0-14.4 (6.9-11.8)
Overijssel	6.3 (3.1)	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)	10.5 (5.4)	8.9-12.2 (4.3-6.6)
Flevoland	4.7 (3.0)	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)	15.3 (8.6)	12.1-18.5 (6.1-11.0)
Gelderland	4.8 (2.8)	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)	9.9 (5.4)	8.7-11.2 (4.5-6.3)
Utrecht	4.9 (2.4)	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)	7.8 (4.7)	6.4-9.2 (3.6-5.7)
Noord-Holland[b]	5.5 (3.5)	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)	8.9 (4.9)	7.7-10.1 (4.0-5.8)
Amsterdam	5.1 (2.4)	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)	8.6 (3.6)	6.7-10.4 (2.4-4.9)
Zuid-Holland[b]	5.6 (3.1)	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)	11.2 (6.0)	10.0-12.4 (5.1-6.9)
Rotterdam	5.3 (3.1)	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)	5.9 (4.2)	4.1-7.7 (2.7-5.7)
Den Haag	6.8 (4.2)	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)	9.2 (5.6)	6.8-11.7 (3.7-7.6)
Zeeland	5.6 (3.7)	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)	12.9 (9.8)	9.5-16.4 (6.8-12.8)
Noord-Brabant	6.4 (3.2)	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)	13.4 (7.9)	12.1-14.7 (6.9-8.9)
Limburg	6.2 (3.9)	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)	10.5 (6.0)	8.7-12.3 (4.6-7.4)
Netherlands	5.6 (3.1)	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)	10.7 (6.1)	10.3-11.2 (5.8-6.5)

[a] For 2001, 2002, 2003 and 2004 coverage data for 2001 have been used.
[b] provinces without the three big cities (Amsterdam, Rotterdam, Den Haag)



based on the birth cohort 2001
& the mean of 2001, 2002 and 2003, based on the birth cohort 2001
* provinces without big cities Amsterdam, Rotterdam, Den Haag

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

The 95% confidence intervals for the rates in the different regions contained the country's overall reporting rate in eight of the fifteen regions. For major events only this number is seven. The country's average reporting rate for major events is 6.1/1000. This is higher than 2002 and 2003 (3.5/1000). We will present and compare differences in numbers of specific events in the respective paragraphs under 6.8. For more information see table 6 and figure 2.

6.4 Vaccines

In 2004 most notifications were about recent vaccinations (all except 78). Some of these 78 late reports, (33 in 2003), arose from concerns about planned booster vaccination or vaccination of younger siblings. This year reporters frequently mentioned that reporting was done because of adverse publicity in the media. In 28% of these cases the parents reported. The vaccine involved in these late reports was most often DPTP-Hib (41 with 20 concerning

the first dose) and MenC (19). 15 Reports stemmed from the active study after ITP (through NSCK) that was analysed in 2004. All reports are included in the tables.
In table 7 scheduled vaccines and actually administered vaccines are listed. As in previous years, reports on the first DPTP-Hib dose were the most prevalent (725 compared to 462 in 2003), with lower numbers on subsequent vaccinations at older age, respectively 379, 289, and 340 for second, third and fourth dose. The relative frequencies of involved vaccinations are similar to previous years (figure 3). The total number of reported adverse events after DPTP-Hib doses was 1730, significantly higher than in 2003 (1019) and 2002 (999).
149 Children received HepB vaccine simultaneously with 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 and we also received two reports on adverse events following neonatal HepB immunisations.

Table 7. Schedule and vaccines of reported AEFI in 2004

vaccine given⇒ scheduled ⇓	dptp	dptp hib	dptp hib hepb	hib	hepb	dptp hib mmr menc	mmr	mmr menc	dtp	ak	dtp ak	dtp mmr	menc	bcg	other	total 2004	2003	2002	2001	2000
at birth	-	-	-	-	2[a]	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-
dptp1+hib1	3	628	93	1	-	-	-	-	-	-	-	-	-	-	-	725	462	503	515	418
dptp2+hib2	2	373	4	-	-	-	-	-	-	-	-	-	-	-	-	379	229	212	229	191
dptp3+hib3	1	265	21	2	-	-	-	-	-	-	-	-	-	-	-	289	147	150	163	133
dptp4+hib4	5	303	31[b]	-	-	-	-	-	1	-	-	-	-	-	-	340	193	161	172	166
dose?	1	2	-	-	-	-	-	-	-	-	-	-	-	-	-	3	3	5	3	6
mmr0	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	1	8	-	4	4
mmr1*	-	-	-	-	-	2	27	192	-	-	-	-	4	-	-	225	173	150	139	141
dtp5+ak	3[c]	4	-	-	-	4[d]	-	-	12	1	66	-	-	-	-	90	78	67	41	33
dtp6+mmr2	-	-	-	-	-	-	-	-	6[e]	-	-	56[f]	-	-	-	62	37	35	47	49
menc	-	-	-	-	-	-	-	-	-	-	-	-	19[g]	-	-	19	34	38	-	-
other	-	-	-	-	-	-	-	-	-	-	-	-	-	2	4[h]	6	10	11	18	1
total	15	1575	149	3	2	6	28	192	19	1	66	56	23	2	4	2141	1374	1332	1331	1142

[a] once hepB and once HBIg
[b] once with mmr0
[c] once also menC
[d] twice no menC
[e] once with hepB
[f] once with hepB, once with hepA and once with hib
[g] all late reports from campaign in 2002
[h] twice influenza, once hepA and once palivizumab

Reports of AEFI following other RVP vaccines increased also. Numbers are much lower however. Since the addition of MenC to the programme in 2002, simultaneously with MMR1 there has been an ongoing increase in reports; the same applies for reports after DTP5 at the age of four years since the introduction of simultaneous aK at the end of 2001.
The number of reports of events following DTP6/MMR2 has increased to 62, compared to 37 in 2003. Late reports of MenC in the campaign (19) are included in this report. The reported adverse events of the MenC campaign have been published separately [52]. Six children were reported with AE following non-RVP vaccines only. Further details in table 7 and figure 3. Specific vaccines and number of reports are listed in table 9.

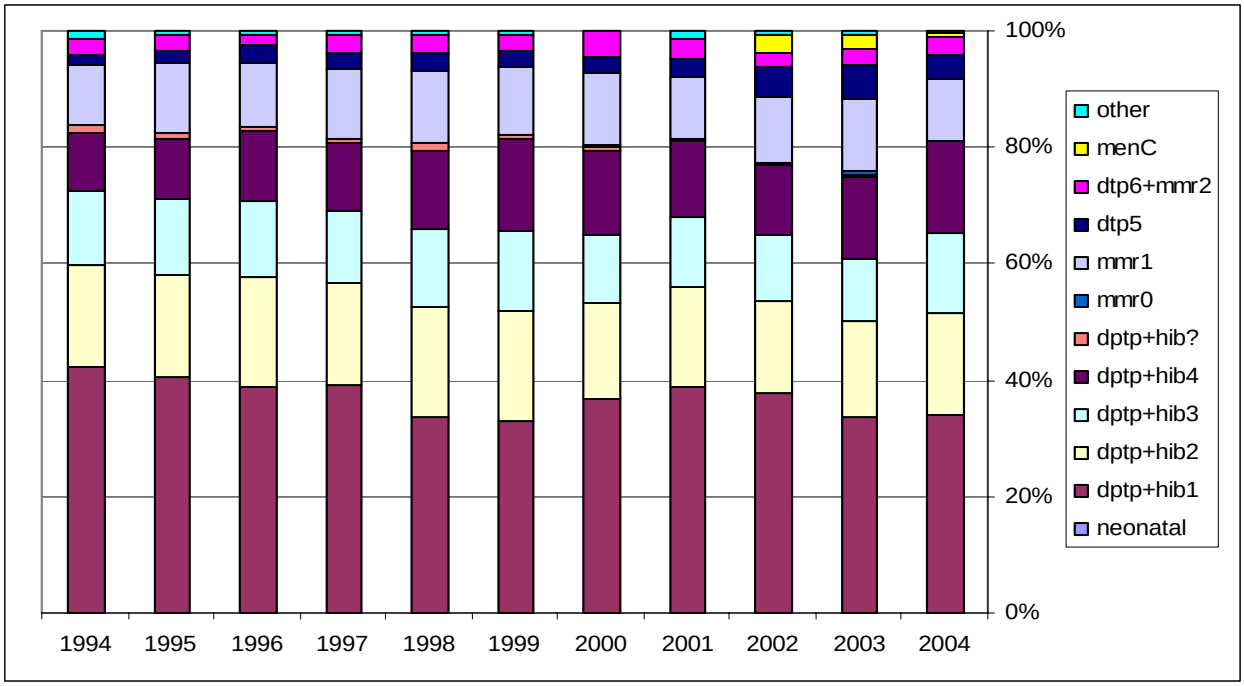


Figure 3. Relative frequencies of vaccine doses in reported AEFI in 1994-2004

Event categories are not equally distributed over the (scheduled) vaccinations (table 8). Faints, mainly collapse, and discoloured legs are most often reported after the first vaccinations, as is persistent screaming. This is consistent over the years. Convulsions, especially febrile, are reported more frequently after the fourth DPTP-Hib and the first MMR/MenC, than at younger ages. No children with anaphylactic shock were reported. Three children with encephalopathy and four 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.

Table 8. Event category and (scheduled) vaccine dose of reported AEFI in 2004 (irrespective of causality)

event ⇓ vaccine⇒*	at birth	dptp hib1	dptp hib2	dptp hib3	dptp hib4	dptp hib?	mmr0	mmr1 menc	dtp5 ak	dtp6 mmr2	menc	other	total 2004	2003	2002	2001	2000
local reaction	-	28	14	14	30	1	-	4	21	15	-	2	129	123	120	90	75
general illness minor	-	244	111	104	110	1	1	89	26	14	4	-	704	460	417	447	366
major	-	26	21	23	67	1	-	37	4	5	10	-	194	119	112	74	106
persistent screaming	-	78	30	12	13	-	-	-	-	-	-	-	133	55	46	49	39
skin symptoms	-	23	12	11	12	-	-	25	11	8	1	3	106	104	104	73	75
discoloured legs	-	108	93	57	15	-	-	1	4	1	-	-	279	134	137	175	126
faints	1	198	84	44	13	-	-	1	19	18	-	-	378	244	297	293	239
fits	1	20	13	23	80	-	-	65	5	1	3	-	211	132	91	121	112
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	1	1	-	-	-	-	-	-	1	-	3	-	-	2	1
death	-	-	-	-	-	-	-	3	-	-	-	1	4	3	8	7	3
total	2	725	379	289	340	3	1	225	90	62	19	6	2141	1374	1332	1331	1142

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

Compared to 2003 and 2002 the total number of reported events has gone up. 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. Preliminary data from the new centralised vaccination register indicate approximately 192,000 third doses of DPTP-Hib in the period covered by this annual report.
The relative frequency of the different event categories is more or less the same over the years (figure 4). General (minor and major) illness is the largest category over the years, with a relative frequency of around 40%.

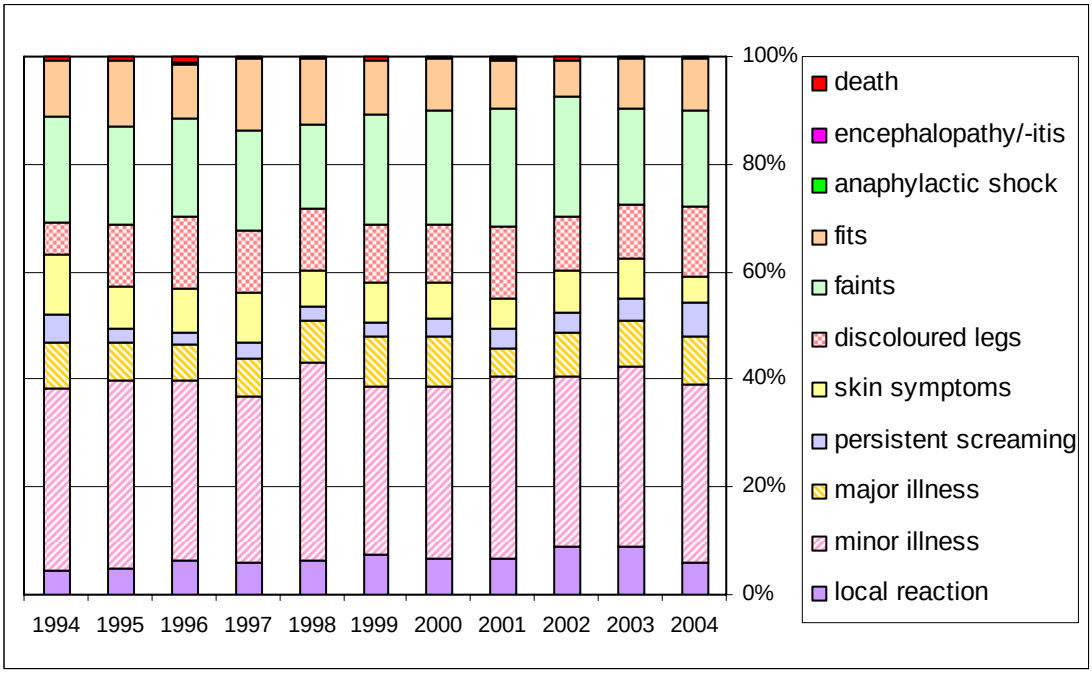


Figure 4. Relative frequencies of events in reported AEFI 1994-2004

The age distribution is (again) given in figure 5, comparing 1998 under the old schedule and 2000-2004, reflecting the new schedule in the age at vaccination 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.

Table 9. Specific vaccines and number of reported AEFI in 2002-2004

vaccine, single or in combination	reports in 2004	2003	2002
dptp	1745	1037	1021
hib	1734	1029	1031
mmr	283	222	188
menC	220	173	55
dtp	141	108	99
aK	67	67	56
hepB	153	55	3
other	8	10	11

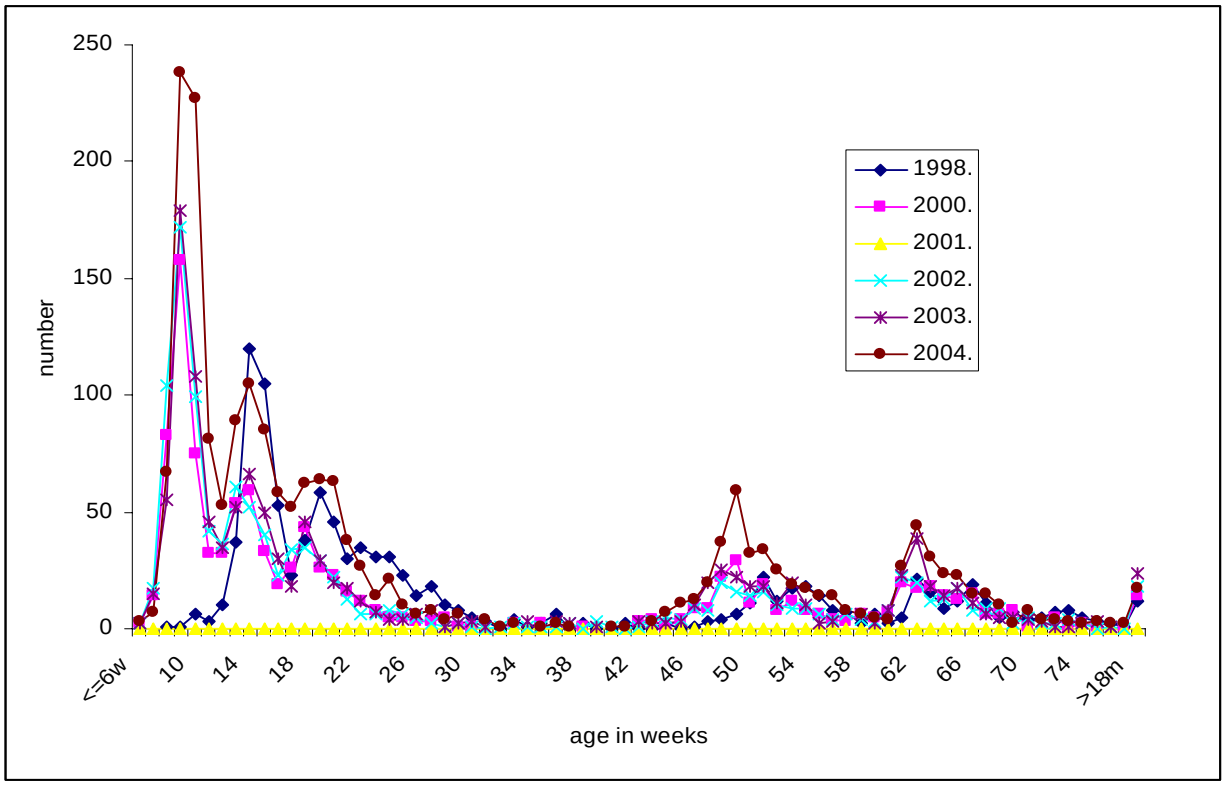


Figure 5. Age distribution of reported AEFI in 1998 and 2000-2004 accelerated schedule

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 (1227 of 2141, 57%, with positive causality 48%) was a little higher than in 2003 (52% and 43%) and 2002 (54% and 47%), figure 6. See also for causality paragraph 6.7.

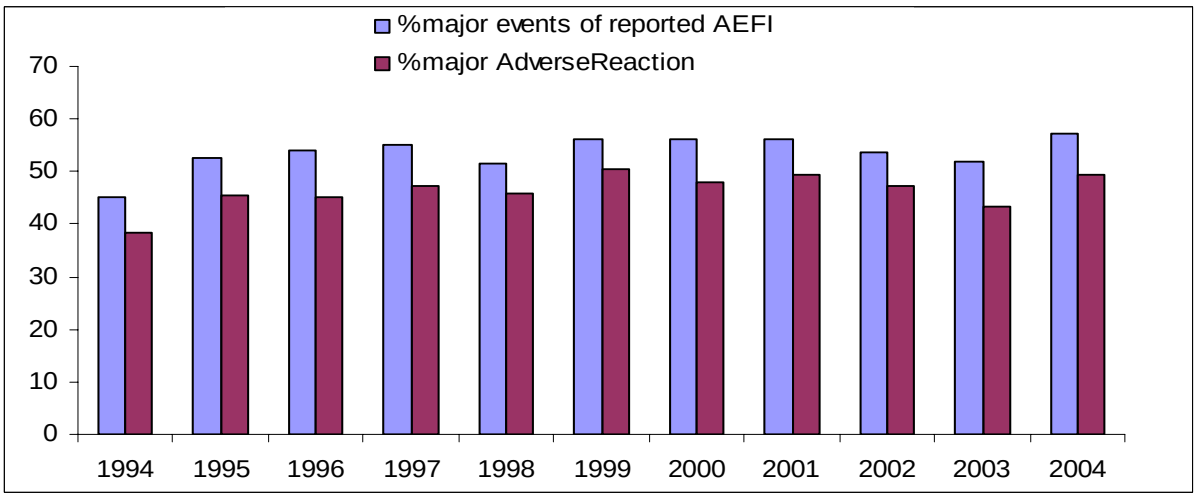


Figure 6. Proportion of reported major AEFI and major Adverse Reactions in 1994-2004

The level of medical intervention may also illustrate the impact of adverse events. In 16% (347) of reports either no medical help was sought or was not reported or recorded by us (range 19-22% for 2000-2004). Nearly 27% of the parents (570) administered paracetamol suppositories, diazepam by rectiole or some skin ointment for instance (range 12-15% for 2000-2004). This apparent higher percentage parallels the decrease in the number of reports lacking specific information on intervention. Table 10 and figure 7 show intervention according to highest level of intervention. 57% of the parents contacted the clinic or GP, called the ambulance or went to hospital, with 8% admittance. For the four previous years these percentages ranged from 60-66% and from 10-13% for hospital admittance.

Table 10. Intervention and events of reported AEFI in 2004 (irrespective of causality)

event⇓ intervention⇒	?	none[a]	supp[b]	clinic[c]	gp tel[d]	gp visit[e]	ambu lance[f]	out-patient	emerg ency	hospital stay	other[g]	post mortem	total
local reaction	10	10	33	17	9	35	-	10	2	3	-	-	129
general illness minor	59	88	217	34	46	169	2	38	14	23	14	-	704
major	5	1	41	1	26	49	-	25	5	40	1	-	194
persistent screaming	9	7	86	1	6	18	-	1	3	2	-	-	133
skin symptoms	7	11	5	9	9	40	-	15	3	2	5	-	106
discoloured legs	14	42	102	18	29	45	1	7	14	5	2	-	279
faints	9	61	57	48	36	87	4	14	17	43	2	-	378
fits	5	9	29	2	12	50	22	18	16	48	-	-	211
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	-	-	-	-	-	-	3	-	-	3
death	-	-	-	-	-	-	-	-	-	3	-	1	4
total 2004	118	229	570	130	173	493	29	128	74	172	24	1	2141

[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

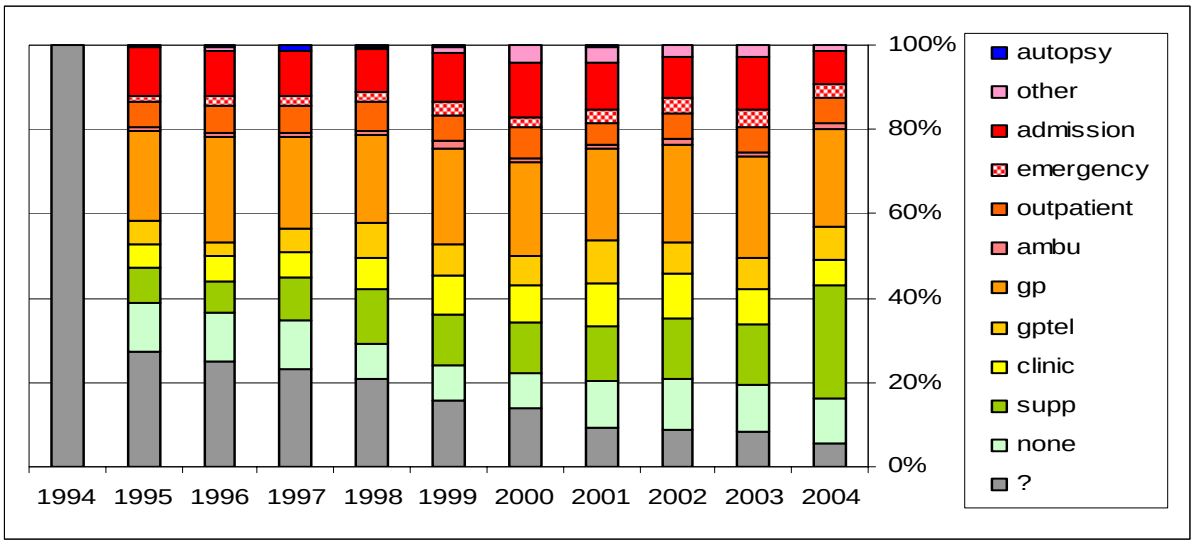


Figure 7. Level of medical intervention for AEFI 1994-2004

6.6 Sex Distribution

Over the years more boys than girls have been reported. Gradually this has “normalised”. In 1994 and before reports concerned boys in 60% of cases, with a gradual decrease from 1995 to 1998 to 54%. Since then this percentage of reported boys ranged between 51-54%. In 2004 54% of reports concerned boys (table 11 and figure 8). Distribution over the different events ranged from 48% boys for local reaction to 63% boys with atypical attacks, with events with less than 40 reports excluded. Of 4 children the sex is not known. See for specifics on the events and subdivision, the respective categories under paragraph 6.8.

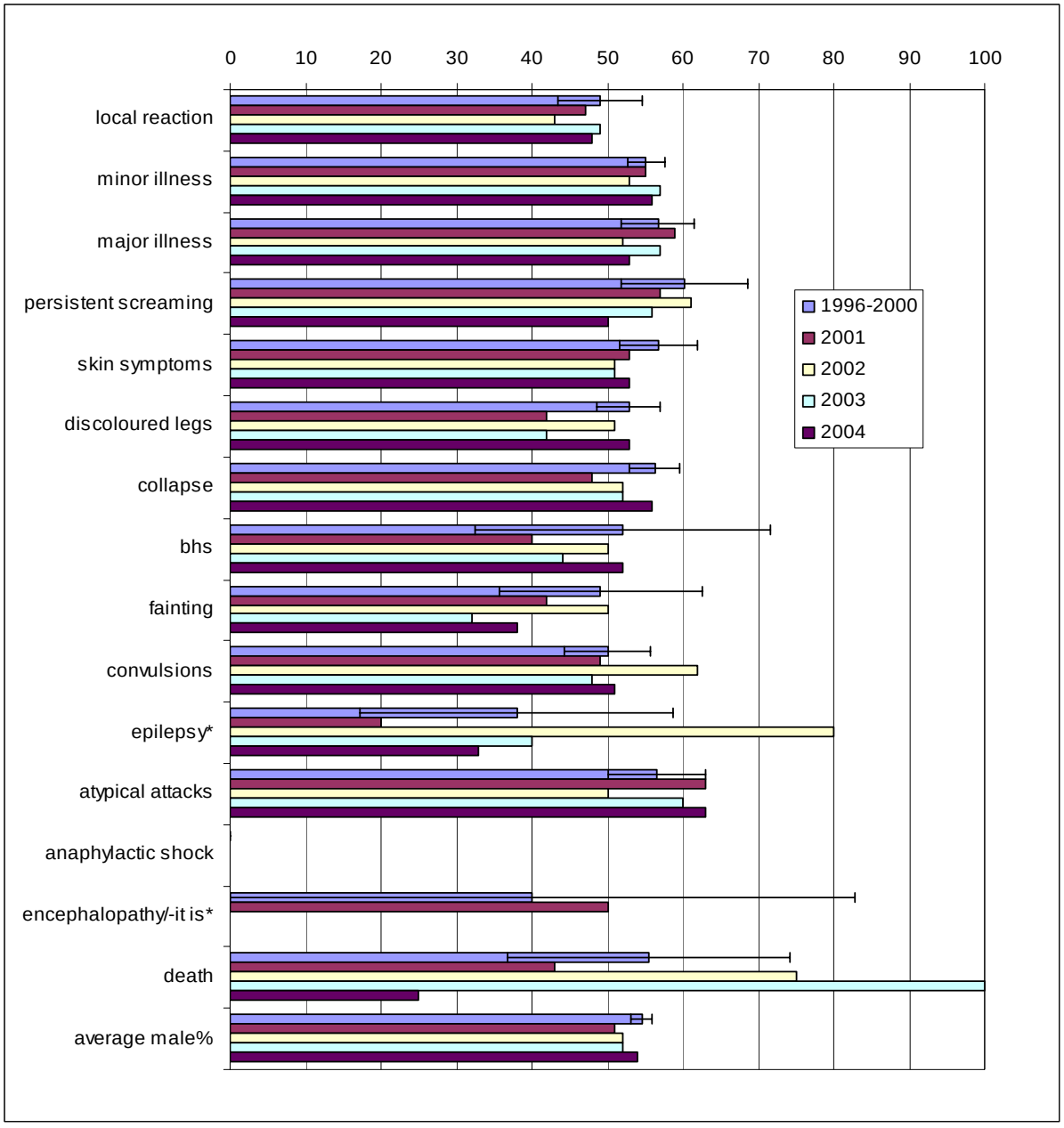


*Figure 8. Events and sex ratio in reported AEFI in 2004, 2003, 2002, 2001 and 1996-2000 with confidence intervals (proportional with exact distribution for *)*

Table 11. Events and sex of reported AEFI in 2000-2004 (totals and percentage males)

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

6.7 Causal Relation

Events with (likelihood of) causality assessed as certain, probable or possible are considered adverse reactions (AR). In 2004, 83% of the reports were adverse reactions, with exclusion of the non-classifiable events. This is a little higher than in 2003, but within the range of 1994-2003 (78-84%). The other events were considered coincidental events with improbable or absent causal relation with the vaccinations. Nine notifications were not classifiable.
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 2004 (% adverse reaction)

event ⇓		causality⇒	certain	probable	possible	improbable	non classifiable	total	(% AR*)
local reaction			73	40	14	2	-	129	(98)
general illness	minor		-	323	231	143	6	704	(79)
	major		-	45	74	75	-	194	(61)
persistent screaming			-	114	15	4	-	133	(97)
skin symptoms			-	4	49	53	-	106	(50)
discoloured legs			-	242	24	12	1	279	(96)
faints	collapse		-	286	18	14	-	318	(96)
	BHS		-	17	3	3	-	23	(87)
	fainting		-	29	7	1	-	37	(97)
fits	convulsions		-	33	47	18	-	98	(82)
	epilepsy		-	-	-	9	-	9	(0)
	atypical attacks		-	29	48	26	1	104	(75)
anaphylactic shock			-	-	-	-	-	-	(-)
encephalopathy/-itis			-	-	-	3	-	3	(0)
death			-	-	-	4	-	4	(0)
total 2004			73	1162	530	367	9	2141	(83)

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

For MMR vaccination nearly 57% of 283 reported adverse events were considered adverse reactions in 2004. This is within the range of the four previous years (53-60%). For DTP, DPTP, Hib, aK, MenC, HepB (including a few HepA and Influenza) vaccinations, possible causal relation was assessed in 78% of the reports. Range for 2000-2003 was 72-87%.

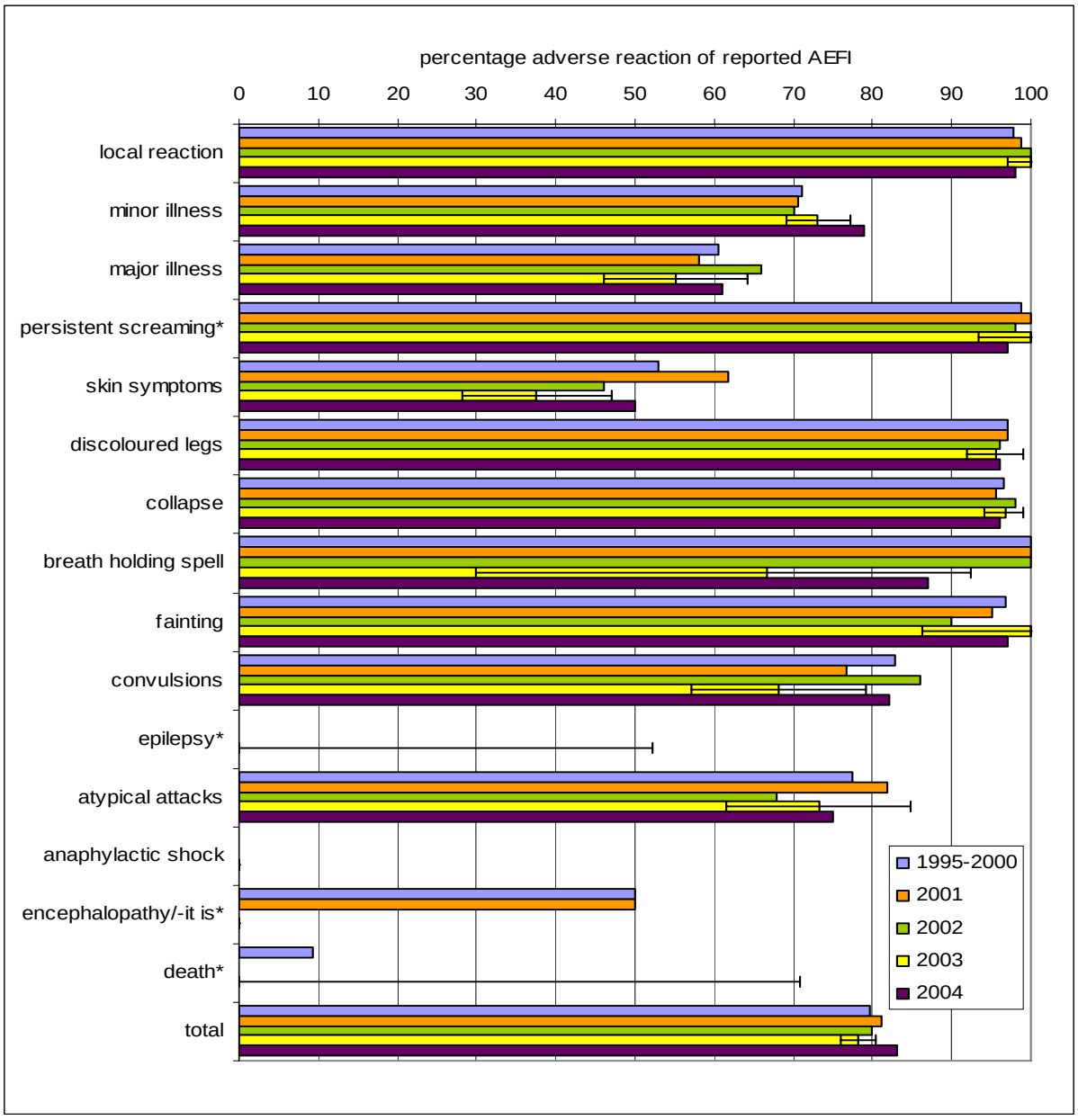


Figure 9. *Causality and events of reported AEFI in 2004 compared to 2003, 2002, 2001 and 1995-2000 (with 95% confidence intervals for 2003, proportional with exact approximation*)*

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 remain "empty" because no events were reported in 2003.

6.8.1 Local reactions

In 2004, 129 predominantly local reactions were reported in approximately equal frequencies after DPTP-Hib or DTP vaccinations (table 13). Nearly all reported local events were considered adverse reactions, i.e. certainly, probably or possibly causally related with the vaccination. Two reports are classified as coincidental
The majority of the reported local reactions (105) were classified as minor reactions.
24 Reports were considered major local reactions because of size, severity, intensity or duration. Common inflammation was most prevalent in 75 reports (10 considered major). The atypical local symptoms (29) were some kind of local rash or discoloration, possible infection, (de)pigmentation, haematoma/fibrosis, only swelling, itch or pain, atypical time interval or combination of these atypical symptoms. 17 Children had marked reduction in use of the limp with mild or no signs of inflammation (one major). This is booked separately as "avoidance behaviour".

Table 13. Local reactions and vaccines of reported AEFI in 2004 (major events)

vaccine⇒ / event⇓	dptp hib1 (major)	dptp hib2 (major)	dptp hib3 (major)	dptp hib4 (major)	dptp hib? (major)	mmr1 menc (major)	dtp5 ak (major)	dtp6 mmr2 (major)	other (major)	2004 (major)	2003 (major)	2002 (major)	2001 (major)	2000
moderate/ pronounced	15[a](3)	7 (1)	3 (0)	11[c] (1)	1 (0)	1 (0)	8[e] (1)	13[f] (3)	1[g] (1)	60(10)	75(13)	54(8)	34(5)	36
absces[s]	6[b] (6)	1(1)	5[a] (5)	2 (2)	-	-	-	-	-	14(14)	6(6)	8 (8)	13(13)	9
pustule	-	-	-	-	-	-	-	-	1[h] (0)	1(0)	0	1(l)	3(3)	nr
atypical reaction	4[a] (0)	3 (0)	3 (0)	4 (0)	-	3[d] (0)	10[f] (0)	2[f] (0)	-	29(0)	24(2)	31(3)	22(1)	25
haematoma	-	1 (0)	1 (0)	-	-	-	-	-	-	2(0)	2(0)	2(1)	6(1)	nr
nodule	2 (0)	-	-	4 (0)	-	-	-	-	-	6(0)	4(0)	17(1)	6(2)	nr
avoidance	1[a] (0)	2 (0)	2[a] (0)	9[c] (1)	-	-	3[c] (0)	-	-	17(1)	12(2)	7(0)	6(0)	5
total (major)	28 (9)	14 (2)	14 (5)	30 (4)	1 (0)	4 (0)	21 (1)	15 (3)	2 (1)	129(25)	123(23)	120(22)	90(25)	75(21)

[a] once with hepB
[b] three times with hepB
[c] once dptp only
[d] once menC only
[e] twice dtp only
[f] once dtp only
[g] influenza
[h] bcg

Nine of the fourteen abscesses were drained surgically; the other five drained spontaneously. To our information five times cultures were taken with two positive for Streptococcus Group A, one for Pneumococcus and another for an anaerobic Streptococcus. 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 depending on severity subdivided in minor or major.

Minor general illness

In 704 children the complaints were considered minor illness in 2004. In recent years the reporting rates have remained stable, but this year the number of reported events has increased. 21% of these reports were considered to have improbable causal relation with the vaccination. This is lower than in the four previous years (range 27-33%). See table 14 and figure 9.

81% of reported events concerned the scheduled DPTP-Hib vaccinations. Compared to previous years the relative share of the subsequent DPTP-Hib doses is stable. See also table 14. For comparison the numbers of 1994-2003 are included.

Table 14. Minor illness and vaccines of reported AEFI in 1994-2004

scheduled vaccine⇓	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	(%AR*)
dptp-hib1	104	102	85	100	117	102	120	158	141	153	244[a]	(89)
dptp-hib2	53	54	47	53	81	75	53	65	72	73	111[b]	(86)
dptp-hib3	37	46	34	42	60	58	45	56	41	52	104[c]	(74)
dptp-hib4	13	27	32	23	54	60	55	63	58	65	109[d]	(77)
dptp-hib?	nr	3	1	2	6	5	1	1	3	2	1[e]	(0)
dptp-hib4+mmr1	nr	2	3	1	-	2	2	3	3	1	1[f]	(100)
mmr1+menC	20	31	32	22	62	55	54	63	51	78	90[g]	(63)
dtp5+aK	3	6	9	3	11	7	13	16	20	11	26[h]	(62)
dtp6+mmr2	5	9	1	7	12	8	23	15	8	8	14	(50)
menC	-	-	-	-	-	-	-	-	17	14	4	(25)
other	7	-	-	1	2	1	-	7	3	4	0	(-)
total	242	280	244	254	405	373	366	447	417	460	704	(79)

* percentage AEFI considered adverse reactions

[a] 37 with hepB and twice dptp only
[b] three times with hepB and once dptp only
[c] six times with hepB and once hib only
[d] seven times with hepB, once dptp only and once dtp only
[e] dptp only
[f] dptp-hib with hepB and mmr0
[g] 11 mmr only (once mmr0) and twice menC only
[h] once dptp only, twice dptp-hib, once dptp-hib and mmr, once dptp-hib with mmr and menC, twice dtp only

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

In 212 reports fever is the most prominent symptom. In 181 cases the fever was considered possibly causally related. In 179 reports of the other (working)diagnoses fever was an important accompanying symptom. Crying was the main feature in 157 reported cases predominantly following the first two vaccinations.

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

Table 15. Main (working) diagnosis or symptom in category of minor illness of reported AEFI in 2000-2004 (with number of adverse reactions)

symptom or diagnosis	2000	2001	2002	2003	2004	(AR*)	symptom or diagnosis	2000	2001	2002	2003	2004	(AR*)
fever	71	87	70	100	212	(181)	pallor and/or cyanosis	52	77	79	89	83	(82)
low temperature	1	5	2	2	2	(2)	abnormal liver enzymes	-	1	1	1	1	(0)
crying	42	51	51	59	157	(150)	rash (illness)	22	25	21	37	34	(7)
groaning	1	1	1	-	2	(2)	vaccinitis	17	21	20	31	31	(31)
irritability	5	5	4	-	6	(3)	parotitis	5	2	3	-	2	(2)
meningismus	-	3	1	-	-	(-)	infectious disease	3	2	1	2	2	(0)
hypertonia	1	1	1	2	3	(-)	swelling face/hands/feet/?	5	6	4	3	8	(4)
myoclonics	21	20	16	21	26	(26)	lymphadenopathy	4	3	2	1	-	(-)
chills	10	14	12	18	20	(20)	arthralgia/arthritis/coxitis/ limping/falling/disbalance/ pain in limbs	3	6	6	8	6	(2)
bulging fontanel	-	1	-	2	1	(1)	allergy/atopy	2	1	2	1	-	(-)
head circumference ⇑ ⇑	-	-	1	-	1	(-)	feeding problems	4	8	4	1	2	(2)
listlessness/fatigue	5	3	4	7	-	(-)	anaemia	-	-	1	-	1	(0)
drowsiness	4	4	2	5	4	(4)	vomiting/nausea	4	6	4	4	1	(0)
prolonged/deep sleep	4	9	7	8	6	(4)	stomatitis/abscess	1	1	3	1	-	(-)
behavioural problem/- illness	10	13	19	6	12	(5)	constipation	2	-	2	1	-	(-)
sleeping problems	5	2	2	2	4	(3)	gastro-enteritis/diarrhoea	11	13	20	14	24	(3)
apnoea/low oxygenation	1	-	2	2	3	(1)	myoglobinuria?		2	7	-	4	(4)
asthma (attack)/cara	4	7	1	2	-	(-)	epidiydimitis/urinary tract infection/haematuria	2	1	1	-	1	(0)
airway infection	10	9	12	8	13	(0)	epistaxis	1	1	-	-	-	(-)
cough	7	4	6	4	4	(0)	headache/migraine/ dizziness	-	2	4	4	3	(0)
dyspnoea/wheezing	6	4	2	3	6	(1)	eye turn/nystagmus/ squint/ anisocoria/abducensparesis /conjunctivitis/photofobia	2	3	4	1	2	(1)
pseudocroup	2	2	1	-	-	(-)	heart murmur/arythmia	-	-	-	1	1	(1)
tonsillitis/cold	1	3	-	-	2	(0)	lying still/frozen	8	9	6	4	10	(10)
otitis	6	2	1	3	-	(-)	undefined transient episode	-	3	1	-	1	(0)
hyperventilation	2	-	-	-	-	(-)	not specified	6	4	3	2	3	(0)
							total minor events	366	447	417	460	704	(554)

* number of adverse reactions

Major general illness

In 2004 major general illness was recorded 194 times, compared to 119 in 2003, 112 in 2002 and 74 in 2001. The distribution in the major illness group is more even over the scheduled vaccines than in the minor illness group. Overall, 119 events were considered adverse reactions (61%). In 2000-2003 this percentage ranged between 54-65%.

MMR was involved in 41 reports with in 12 cases assessed causality (29%, range for 2000-2003 was 41-66%); none of these events was attributable to vaccines given simultaneously. For other vaccines or combinations 107 (57%) reported events were considered to be possible adverse reactions. The range for 2000-2003 was 38%-69%.

Very high fever (≥40.5°C) was the working diagnosis in 123 cases. More than double the number of last year, mainly an increase of events following DPTP-Hib vaccination. 85% of these fever cases were causally related to the vaccination. In the other events in this category very high fever was present in 15 cases. These included the cases with chills/myoclonics and vaccinitis/rash illness, 3 cases of dehydration/gastro-enteritis and 1 case of lower airway infection. ITP (Idiopathic Thrombocytopaenic Purpura) was reported 15 times, all through

the Netherlands Paediatric Surveillance Unit (NSCK). The cases following MMR1 (3) were considered possibly causally related. The 12 reported ITP events following other vaccines were all considered chance occurrences. See for more information table 16 and 17.

Table 16. Major illness and vaccines of reported AEFI in 2004 (adverse reactions)

diagnosis⇓ vaccine⇒	dptp hib1	dptp hib2	dptp hib3	dptp hib4	dptp hib?	mmr1 menC	dtp5 aK	dtp6 mmr2	menC	total (AR*)
high fever	19[a]	17[b]	13[b]	54[c]	-	13	3[e]	2[f]	2	123 (105)
chills/myoclonics	-	-	-	5	-	-	-	-	-	5 (5)
bulging fontanel	-	-	1	-	-	-	-	-	-	1 (0)
dehydration /gastro-enteritis	-	-	2[b]	2	-	3	-	-	-	7 (1)
pneumonia/bronchiolitis/respiratory infection	1[b]	2	1	1	1	-	-	-	-	6 (0)
ALTE	1	-	1	-	-	-	-	-	-	2 (0)
meningitis	2	-	-	-	-	1	-	-	-	3 (0)
vaccinitis/rash illness	-	-	-	-	-	6	-	-	-	6 (5)
cardiomyopathy	1	-	-	-	-	-	-	-	-	1 (0)
arthritis/osteomyelitis/spondylodiscitis	-	-	-	-	-	4[d]	-	-	-	4 (0)
lymphadenitis mesenterica/intussusception	-	-	-	-	-	1	-	1	-	2 (0)
ITP	-	1	1	2[b]	-	3[d]	-	2[e]	6	15 (3)
Kawasaki	-	-	1	1	-	-	-	-	-	2 (0)
diabetes mellitus	-	-	-	-	-	2[d]	-	-	-	2 (0)
Aicardie syndrome	1	-	-	-	-	-	-	-	-	1 (0)
retardation/autism	-	-	2[b]	2	-	1[d]	-	-	-	5 (0)
urinary tract infection/nephrotic syndrome/ Henoch Schönlein	1	1	-	-	-	2	1	-	1	5 (0)
plexus neuritis /guillain barré	-	-	-	-	-	1	-	-	1	2 (0)
shaken baby syndrome	-	-	1	-	-	-	-	-	-	1 (0)
total 2004 (adverse reactions)	26	21	23	67	1	37	4	5	10	194 (119)

* number of AEFI considered adverse reactions

[a] four times with hepB
[b] once with hepB
[c] seven times with hepB
[d] once mmr only
[e] once dtp only
[f] once with hepA

Table 17. Major illness and causal relation of reported AEFI in 2004

diagnosis⇓ causality⇒	certain	probable	possible	improbable	unclassifiable	total (AR%)
high fever	-	43	62	18	-	123 (85)
chills/myoclonics	-	2	3	-	-	5 (100)
bulging fontanel	-	-	-	1	-	1 (0)
dehydration /gastro-enteritis	-	-	1	6	-	7 (14)
pneumonia/bronchiolitis/respiratory infection	-	-	-	6	-	6 (0)
ALTE	-	-	-	2	-	2 (0)
meningitis	-	-	-	3	-	3 (0)
vaccinitis/rash illness	-	-	5	1	-	6 (83)
cardiomyopathy	-	-	-	1	-	1 (0)
arthritis/osteomyelitis/spondylodiscitis	-	-	-	4	-	4 (0)
lymphadenitis mesenterica/intussusception	-	-	-	2	-	2 (0)
ITP	-	-	3	12	-	15 (20)
Kawasaki	-	-	-	2	-	2 (0)
diabetes mellitus	-	-	-	2	-	2 (0)
Aicardie syndrome	-	-	-	1	-	1 (0)
retardation/autism	-	-	-	5	-	5 (0)
urinary tract infection/nephrotic syndrome/ Henoch Schönlein	-	-	-	5	-	5 (0)
plexus neuritis /guillain barré	-	-	-	2	-	2 (0)
shaken baby syndrome	-	-	-	1	-	1 (0)
total 2004	-	45	74	75	-	194 (61)

6.8.3 Persistent Screaming

In 2004, 133 children with persistent screaming were reported (in 1994-2003 this number ranged between 16 and 55). Persistent screaming appears again age/dose dependent, as has been noticed in former years (see table 9). Additional symptoms were pain and swelling at injection site, restlessness, pallor, myoclonic jerks and fever. Parents were usually desperate; 24 contacted the family physician and six children were admitted in hospital. We did not record the degree of intervention in nine cases, however (table 9). In all but four 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

In 2004 skin symptoms were the main or only feature in 106 reports, similar to 2003 and 2002 (104). Discoloured legs are not included but are categorised separately. The numbers are considerably higher than in prior years (range 73-85 for 1997-2001) with increase mainly in reported AEFI following MMR1 and DTP5/aK vaccinations. The number of reports considered adverse reactions was 53, higher than in 2003 and 2002 with 38 and 47, respectively. See table 18.

Table 18. Skin symptoms and vaccines of reported AEFI in 2004 (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	2	1	1	1[b]	2	2	-	1	-	10	(6)
exanthema	9[a]	7	4	5[b]	19[d]	6[f]	6	-	3[g]	59	(30)
itch	-	-	-	-	-	1	-	-	-	1	(0)
abscess/ulcus	1	-	-	1	-	-	-	-	-	2	(0)
erythema	-	-	1	-	-	-	-	-	-	1	(1)
blue hands/red fingers	2	-	-	-	-	-	-	-	-	2	(2)
harlequin	-	1	-	-	-	-	-	-	-	1	(1)
blisters	-	-	1[c]	-	-	-	-	-	-	1	(0)
red lump back	1[b]	-	-	-	-	-	-	-	-	1	(0)
teleangiectasia/ naevus	1	-	-	-	1[e]	-	-	-	-	2	(0)
urticaria	-	1	1	2	2	1	1	-	-	8	(4)
eczema (increase)	6	1	2	2	1	-	1	-	-	13	(7)
petechiae /purpura	1[b]	1	1	1	-	1	-	-	-	5	(2)
total 2004	23	12	11	12	25	11	8	1	3	106	(53)

* number of AEFI considered being adverse reactions
[a] twice with hepB
[b] once with hepB
[c] once hib only
[d] three times mmr only
[e] once mmr0 only
[f] once dptp-hib and mmr and once dtp only
[g] bcg, influenza and hepA

All reports were considered minor skin manifestations.
Exanthema, angio-oedema/swelling and (increased) eczema were the most frequent symptoms, amounting to 77%. Eight times urticaria were reported. Five reported children had petechial rash on upper body and/or face. Children with petechiae on the legs only are categorised under discoloured legs.

34 Cases concerned MMR, 30 times combined with DPTP-Hib, MenC or DTP. In 50% there was a possible causal relation with MMR (range 35-77% for 2000-2003). For the other vaccines or combinations, possible causal relation was assessed in 44 out of 101 events, 43% within the range for the four previous years 32-57%. See table 19.

Table 19. Skin symptoms and causal relation of reported AEFI in 2004

causality⇒ / symptom⇓	certain	probable	possible	improbable	unclassifiable	total	(%AR*)
angio-oedema/swelling	-	-	6	4	-	10	(60)
exanthema	-	2	28	29	-	59	(51)
itch	-	-	-	1	-	1	(0)
abscess/ulcus	-	-	-	2	-	2	(0)
erythema	-	1	-	-	-	1	(100)
blue hands/red fingers	-	-	2	-	-	2	(100)
harlequin	-	1	-	-	-	1	(100)
blisters	-	-	-	1	-	1	(0)
red lump back	-	-	-	1	-	1	(0)
teleangiectasia/ naevus	-	-	-	2	-	2	(0)
urticaria	-	-	4	4	-	8	(50)
eczema (increase)	-	-	7	6	-	13	(54)
petechiae /purpura	-	-	2	3	-	5	(40)
total 2004	-	4	49	53	-	106	(50)

* percentage of AEFI considered being adverse reactions

6.8.5 Discoloured legs

Starting from 1995, discoloured legs are listed in a separate category, subdivided in blue, red or purple legs with diffuse or patchy discoloration, with or without petechial rash. Leg petechiae without noted discoloration are also grouped in this category. From 2001 onward also swollen limbs with or without discoloration after the fifth dose of DTP an aK are included.

In 2004, 279 reports were received, again a sharp increase compared to 2003. (134 in 2003, 137 in 2002, 175 in 2001 and 126 in 2000; table 19). Of these reports 36 were blue legs (25 double-sided), 130 red legs (46 double-sided) and 69 purple legs (44 double-sided). In total, 74 reported leg petechiae, with or without prior discoloration ranged in numbers from 31-48 in the four previous years.

52% (144) of the reported children had also fever. Five times the temperature was ≥40.5°C; these (compound) reports are also listed in the major general illness category. Another 17 reports were compound because the children had also collapse or BHS and are listed in the respective subcategories. Two children had compound reports with both events considered discoloured legs but not considered to be part of the same event. Two children with discoloured legs had also persistent screaming, not considered part of the event but time spaced and therefore also listed under persistent screaming; in the other 11 children with prolonged or persistent crying this was considered part of the discoloured leg syndrome and not listed separately. 81 Children had multiple reports. 71 Of these had recurrent discoloured legs and/or petechiae after subsequent vaccinations. Reported discoloured legs occurred most frequently after the first and second DPTP-Hib vaccinations (72%). Causal relation with the

vaccines was inferred in all but twelve cases; one case was unclassifiable. See table 11 and figure 6.

Table 20. Discoloured legs and vaccines of reported AEFI in 2004

vaccine⇒ symptoms⇓	dptp hib1	dptp hib2	dtpt hib3	dptp hib4	mmr1 menc	dtp5 ak	dtp6 mmr2	petechiae	total 2004	2003	2002	2001	2000
blue legs	15[a]	14	6	1	-	-	-	7	36	29	26	31	23
red legs	51[b]	44	20[d]	10	1	3	1	18	130	51	40	63	46
purple legs	31[a]	17	17	4	-	-	-	8	69	24	43	56	47
petechiae only	9[c]	18	13	-	-	-	-	40	40	26	23	22	9
swollen limb	2[b]	-	1	-	-	1	-	1	4	4	5	3	nr
total 2004	108	93	57	15	1	4	1	74	279	134	137	175	126

[a] four times with hepb
[b] once also hepb
[c] once hib only
[d] twice also hepb

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 2004

vaccine⇒ event⇓	at birth	dptp hib1	dptp hib2	dptp hib3	dptp hib4	mmr1 menc	dtp5 aK	dtp6 mmr2	total 2004	2003	2002	2001	2000
collapse	-	190[b]	78[d]	40[e]	10	-	-		318	210	270	268	221
bhs	1[a]	8[c]	6	4	3	1	-	-	23	9	8	5	5
fainting	-	-	-	-	-	-	19[f]	18[g]	37	25	19	20	13
total 2004	1	198	84	44	13	1	19	18	378	244	297	293	239

[a] hbig
[b] 18 times also hepB
[c] twice also hepB
[d] once dptp only
[e] five times also hepB
[f] five times dtp only and once aK only
[g] once also hepB, once dtp and hepB, twice dtp only

In 2004 collapse was reported in 318 cases. This is an increase compared to the numbers reported in previous years, mainly with respect to the second dose of DPTP-Hib. As we described before, the distribution of collapse over the different scheduled vaccines is in the majority of cases after the first DPTP-Hib vaccinations (60%) and numbers diminishing with dose number and age [35,43,47]. In 2004 19 children were reported with recurrent collapse, some with rather incomplete episodes (range 5-18 for 2000-2003). In 14 children with single collapse reactions the event was assessed as not related because of the too long time interval and/or other causes (range 4-9 for 2000-2004). BHS occurred in 23 reported children; the children turned blue, after stopping to breathe in expiration when crying vehemently or after other stimuli, with a very short phase of diminished responsiveness and no limpness or pallor. Fainting in older children was reported 37 times.
See also tables 11 and 12 and figures 7 and 8 for sex distribution and causality and discussion in chapter 7.

6.8.7 Fits

In this category (febrile) convulsions and epileptic seizures find a place. In the subcategory of "atypical attacks" paroxysmal events are listed in case no definite diagnosis could be made and convulsion could not be fully excluded either. See also paragraph 5.5 for case definitions. Most reported convulsions were febrile (90 out of 98), occurring predominantly after the fourth DPTP-Hib (38) and MMR1/MenC (44) vaccinations. In 75 of these the fever was possibly caused by the vaccination and thus these convulsions were considered adverse reactions. 15 Febrile convulsions were not considered to be causally related, as there was another cause established and/or an implausible time interval with the vaccination. See also table 12. 24 Children had fever of 40.5°C and over, but these were not listed under major illness since the fever was considered part of the event; twice not causally related. In all but two, this very high fever occurred in the one year-olds. See table 11 for sex distribution and table 10 for level of intervention.
Eight non-febrile convulsions were reported. Of the non-febrile convulsions five were considered possibly provoked by the vaccine, the other three considered chance occurrences. All these children had (suspected) epilepsy.
Nine children with epilepsy were reported, of which three had (possible) West syndrome. In none of these children (fever caused by) the vaccine was regarded as trigger.

Table 22. Fits and vaccines of reported AEFI in 2004

vaccine⇒ / event ⇓	at birth	dptp hib1	dptp hib2	dptp hib3	dptp hib4	mmr1 menc	dtp aK	dtp6 mmr2	menc	total 2004	2003	2002	2001	2000
febrile convulsion simple	-	1	1	1	21[e]	19[g]	2[k]	-	-	45	28	22	26	29
complex	-	-	1	3	10[f]	18[h]	-	-	-	32	23	20	21	26
tonic	-	-	-	-	3	2	-	-	-	5	2	-	2	1
atypical/not specified	-	-	-	-	3[d]	3	1[m]	-	1	8	11	3	2	3
non febrile convulsion	1[a]	1	1	2[d]	1	2[i]	-	-	-	8	6	-	5	4
epilepsy	-	-	-	4[d]	2	-	1	1[o]	1	9	5	5	10	7
atypical attack	-	18[b]	10[c]	13	40[e]	21	1	-	1	104	57	41	55	42
total 2004	1	20	13	23	80	65	5	1	3	211	132	91	121	112

[a] hepB
[b] three times with hepB
[c] once dptp only
[d] once with hepB
[e] once dptp only and three times with hepB
[f] three times with hepB
[g] four times mmr only
[h] once mmr only
[i] once mmr only and once menC only
[k] once dptp-hib and mmr and menC
[m] dptp and menC
[o] once with hib

In 2004 atypical attacks were recorded 104 times, with in 77 cases possible causal relation with the vaccination. In this subcategory there were 30 children with possible chills and/or myoclonics and 30 children were hypertonic and/or limp. Nine children had possible breath-holding-spells and four had gastro-intestinal symptoms. In the other 21 the symptoms were very aspecific. None of the children fulfilled the case definitions for collapse or convulsion. The reported atypical attacks were also most frequent after the vaccinations in the one year

olds (table 22). Reported atypical attacks at the younger ages were less frequently accompanied by fever than at later doses/older ages. 14 children had fever of $\geq$40.5^{o}C, three times not causally related to the vaccination.
In 2004 MMR was involved in 66 reports, 59 times with simultaneous inactivated vaccines. Causality of the event with MMR was assumed in 46 cases. Thus there was imputed causal relation of the fits with MMR in 70% of the reports (range 58-80% for 2000-2003). For the other vaccines 54% of the reported events were considered adverse reactions. This is within the range of 2000-2003 (46%-78%).

6.8.8 Encephalopathy/encephalitis

Three events reported in 2004 were listed in this category. All three were considered chance occurrences and not induced or aggravated by the vaccinations. The first child had underlying retardation and epilepsy. She had been free of seizures under anti-epileptic drugs for one year. 2.5 Days after the MenC vaccination (in the campaign in 2002) she had an epileptic fit. Since then her condition deteriorated with uncontrollable seizure activity and encephalopathy. After two years a metabolic disorder was diagnosed. This particular disorder can well explain this severe and erratic course.
The second child developed fever after the third DPTP-Hib and HepB vaccinations. This lasted two days. The following days she became progressively drowsy with decreased milk intake. Five days after the vaccination she was admitted in hospital with asymmetrical muscle tone with forced deviation of the eyes. She had a large infarction affecting the entire right hemisphere. There were extensive intracranial and extracranial arterial anomalies.
The third child received the second DPTP-Hib in hospital. She had been admitted with non-compaction cardiomyopathy. 12 Hours after the vaccination she developed an one-sided convulsion and ptosis of the right eye. This was shown to be caused by infarction in the left hemisphere, probably by an embolus from the heart.

6.8.9 Anaphylactic shock

There were no reports on anaphylactic shock in 2004.
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 2004 four children who died following vaccination, were reported (see table 23). These concerned three girls and one boy. See the case histories below. Twice autopsy was performed, however not in all instances inclusive of full toxicological, microbiologic or metabolic work-up or with post-mortem examination of the brain. Without full post-mortem investigation a definite diagnosis is often not possible. In all four cases death was not judged to be caused or hastened by the vaccination. Three children had severe underlying disease which caused death. In child A death was possibly caused by a side effect of the treatment with anticoagulants. In child C no cause of death could be found. The course was suspect of a metabolic disorder however. The interval between vaccination and the start of the symptoms was too short to implicate MMR and too long too implicate MenC.

Table 23. Death and vaccines of reported AEFI in 2004

child	sex	age[a]	vaccines	time interval illness	time interval death	symptoms/diagnosis	causality[b]	autopsy
A	m	14m	mmr1+menc	9d	1w	cardiac anomaly with xenopatch, Down syndrome, listlessness, rash, seizure, brain infarction, thromboembolus heart, anticoagulants, brain haemorrhage	no	no?
B	f	5m	palivizumab	-	d0	cardiac anomaly, heart failure, fever, hyperthemia, cardiogenic shock	no	no?
C	f	14m	mmr1+menc	4d	6d	fever, vomiting, convulsions, multiorgan failure, metabolic disorder?	no	yes
D	f	14m	mmr1+menc	43d	46d	suspected immune disorder, infection leg, brain oedema, coning, pseudomonas septicaemia	no	yes

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

[b] age at vaccination

Child A

A boy of 14 months old got his MMR and MenC vaccinations. He had Down syndrome and underlying cardiac anomaly. Nine days after the vaccinations he became listless and developed a faint rash on his abdomen. A day later he had swollen glands in his neck. A few days before he got his first tooth. There was no fever. The listlessness increased the next day and the rash covered trunk, face and arms. He developed limpness of one arm and leg and his eyes were averted. The scan showed a brain infarction. This appeared to be caused by a large thrombus on the xenopatch in his heart. He was treated with anticoagulants. Initially he seemed to improve but after a week he died suddenly because of a brain haemorrhage.

Child B

A girl of 5.5 months old received the third dose of palivizumab. She had a severe congenital heart anomaly for which she underwent surgery several times. She suffered from heart failure and had unexplained fever episodes. The day of the injection her condition deteriorated and she developed hyperthermia. She died a few hours later of cardiogenic shock.

Child C

A girl of 14 months of age was vaccinated with MMR and MenC. Four days later she became ill with fever and vomiting. 1.5 Days later she convulsed. On admission in the ICU she had multiorgan failure en signs of encephalitis. The abnormal lab results were pointing to a metabolic disorder, but could also be due to the very bad condition of the child. She died 7 days after the vaccinations. Post mortem examination could not explain the death. Virological screening was negative and no metabolic disorder could be detected.

Child D

A girl of 14 months of age got the MMR and MenC vaccinations. The following weeks were uneventful. She died 46 days after the vaccinations. A few days before she developed fever and a cellulitis-like inflammation on the leg. This was suspect of an infection for which she received anti-biotics. On check-up the next day, she appeared increasingly ill with expansion of the infected spot. She was admitted and referred to a university hospital. The next day she

died of cerebral oedema and subsequent coning. Lab results showed Pseudomonas septicaemia. The girl had had several severe infections before for which she received Bactrimel maintenance therapy in her first year. She had repeatedly granulocytopaenia and was suspected of granulocyte function disorder. Diagnostic work-up had not been completed yet at the time of death.

7 Discussion

The success of the vaccination programme, having brought the target diseases under control, increases the relative importance of side effects [13,14]. This increases the demands on the safety surveillance system likewise. Mere registration and reporting of possible adverse reactions is not enough to sustain confidence in the safety of the programme [62,63,64]. The increased attention of the public and professionals with regard to the safety of vaccines may have adverse consequences for the willingness to participate in the programme. It may also influence the number and the type of adverse events following immunisation reported to the safety surveillance system.
We will discuss the characteristics of the current enhanced passive surveillance system and comment on its strength and weaknesses. We will discuss how the information in the current system may play a role in the management of adverse events and in the risk-benefit communication to professionals and parents.
The Achilles' heel of passive surveillance is underreporting. Especially selective underreporting creates distortion. Therefore the representativeness of data on AEFI presented here, will be discussed.

The year under report was given special attention because of persistent adverse media reports on the safety of the vaccination programme from the first week of 2004 onwards. This caused substantial apprehension in the general public, in the parliament and to some extent also among professionals. These adverse media reports focussed mainly on alleged neurological consequences following the current whole cell pertussis vaccine. The anticipated GR advice on pertussis vaccinations, appeared in April 2004 [3]. This was a revision requested by the Minister of Health because of the continuing high incidence of pertussis in the Netherlands. The GR recommended a shift to an acellular pertussis vaccine for the infants at the earliest possible time. This was based on the assumption that poor effectiveness of the current whole cell vaccine caused the high incidence of pertussis in the Netherlands. GR stressed also the reactogenicity of whole cell vaccine in use. This added substantially to the public concern, although the GR acknowledged that no permanent sequelae were to be feared. The discussion focussed thereafter on so called "very troublesome" adverse events as collapse, convulsions and prolonged crying. GR stated that the majority of these adverse events could be prevented if the whole cell pertussis component was to be substituted. Incidence rates for these "preventable" adverse events from literature, field trials, with varying case definitions, schedules and combinations were extrapolated to the Dutch situation. The resulting numbers were subsequently very confusing.
From the first Monday of the year the telephone information service was flooded with calls from professionals and parents for accurate information on adverse events. The number of contacts doubled and were similar to that during the MenC campaign (2002) and the last polio epidemic (1992-1993) in the Netherlands. Now the consultations focussed more on (supposed) adverse reactions. Estimates as accurate as possible for these more infrequent adverse events were disseminated to the Minister of Health for parliament and by the Director

General of RIVM to professionals and posted on RIVM's website. In April 2004 these topics were also posted on the then launched specific RVP website (www.rvp.nl). Also from the first week of 2004 onwards the number of reported adverse events soared to nearly double the usual, expected numbers. The Ministry of Health was informed immediately about this unprecedented public concern and the possible consequences for the vaccine coverage. Reports of the current year has been carefully monitored for unexpected, unknown, new severe or particular adverse events and to changes in trends and severity. Also the media reports on adverse events were carefully studied and if reports were identifiable they were checked in the safety surveillance system and if necessary included. We monitored also specific websites on cited adverse events.
Below we will discuss different aspects of the increase in number and nature of reported adverse events in 2004.
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 Number of Reports

The number of reports increased sharply as of the first week of 2004. A substantial part of these reports were so called duplicate reports of events already registered in the system. Some of these were thought to be primary reports by the reporter and some were a renewed check on the previous assessment and consequences for subsequent vaccinations (for the child or its siblings). Where appropriate we reassessed these reports. It is worth to mention that all identifiable reports of severe adverse events in the media were already registered in the system, most had also been reassessed by the GR committee. Reporters sometimes reported an event as an afterthought to make up for prior "negligence" as the reporting professionals phrased it. They were often brought to reporting by disturbed parents. Among the reporters were also quite a few parents questioning the role of the vaccinations, especially of children with unexplained health or developmental problems. Only 78 new reports however concerned non-recent vaccinations however, though more than double the number in 2003, in all a very small percentage of the total number of reports.
In the first months the number of reports was higher than in later months (1154 vs 987 in the first and second trimester, respectively) and the content (substance) of the reports shifted also somewhat from neurological events like fits to prolonged crying. The reporting pattern seemed to be dominated by the parliamentary discussions which focused mainly on crying and perhaps also on very high fever and other acknowledged but more rare events.
In the later months of the year the reporting pattern returned more or less to "normal", albeit with apparently a lower threshold with subsequent higher numbers. Apart from some increase in late reports the increase in reports in 2004 was due to quite an increase in compound and multiple reports. This points to increased follow up both by RIVM and spontaneously. In absolute numbers the main body of increase was in the single events. Much more than in previous years the wisdom of further vaccination was questioned, both by parents and professionals. Frequently there was a tendency to regard the occurred adverse event as

contraindication despite the current scientific beliefs. It appeared hard to determine if the reluctance in continuing the programme by professionals was only fuelled by parental choice in the matter. A renewed effort in informing professionals on the scientific state of the art concerning causality and contraindications to vaccination seems warranted.
Below we will discuss the nature and severity of the reported events and the involved vaccine doses.

7.1.1 Distribution over Vaccines and Dose

The increase in reports affected all vaccines of the RVP but did affect DPTP-Hib vaccinations slightly more than the other vaccines. The share of reports concerning DPTP-Hib was 81%, compared to 78% on average for the four previous years (range 75-81%). The first vaccination with DPTP-Hib always has a higher number of reports than the later doses. To some extent this will be because of more concern about the young child and questions about subsequent vaccinations, but the majority is caused by the higher incidence rate of some age specific events. The relative frequency within the four DPTP-Hib doses changed to a little less predominance of the first dose (42% in 2004 and 45% in 2003) with a shift to later doses. The further rise of reports following MMR1 after the inclusion of simultaneous MenC vaccination seems to be due to decreased underreporting and increased willingness to report. The increase in reports following the vaccinations of the four- and nine-year-olds is probably due to reduced underreporting caused by the public apprehension as well.
No new adverse events or increase in severity of events were noted. See for details the following paragraphes.

7.1.2 Distribution over Events

The increase in reports appears to be mainly due to more reports of crying and (very) high fever. Crying is, depending on intensity and duration, listed under general minor illness (increase from 59 to 157) and under persistent screaming (increasing from 55 to 133). Fever is listed under minor general illness (increase from 100 to 212) and for fever $\geq$40.5^{o}C under major general illness (52 to 123). These 359 acknowledged adverse events account for 51% of the total increase in reports.
The number of reported discoloured legs seems to have doubled, but it remains to be seen whether all these reports fit the case definition. Some appear to be very transient or localised events, (see below under the specific event category). The increase in reports on faints were not as much caused by collapse reactions (HHE) of the young infants but mainly due to an increase in reported fainting in the four- and nine-year-olds and to some extent also to an increase in reported breath-holding-spells in infants. In the category of fits there appeared to be some increase in reported febrile convulsions. This increase both for DPTP-Hib4 and for MMR1 does not affect the estimated incidence rate from a data linkage study and a Dutch follow up study, i.e. 1-2 per 10,000 vaccinations. See for further comments the following paragraphs under the specific events. The number of reported non-febrile convulsions and epilepsy remains more or less stable. The considerable increase in non-classifiable paroxysmal events without definite diagnosis, atypical attacks, increasing from 57 to 104,

will be commented upon in the respective event paragraph below. No new or abnormal events were detected in 2004, despite the considerable increase in reports.
ITP from the NSCK surveillance (15) and reports from the active survey on the more severe adverse events (115) contributed only a little to the increase in reports. These reports amounted to only 6% of the total number of reported AEFI.
Like in former years there is a small overrepresentation of boys in the reports, (53.7%, c.i. 51.6 en 55.8, compared to 51.1% in the birth cohorts). There appears to be no systematic change compared to former years.

7.1.3 Severity, Reporting Interval, Causality and Level of Intervention

In the current year the absolute number as well as the relative share of so called major events has gone up. The same applies for causality. This is attributable solely to the increase of persistent screaming, very high fever and febrile convulsions and to the increase of discoloured legs. Those events are by definition booked as major events and are acknowledged adverse reactions. In the reports there is no unexpected or unexplainable increase in severity or in percentage adverse reactions. The number of hospital admissions was equal to 2003 resulting percentage wise in a decrease to 8%. According to this number the relative severity decreased in 2004. Reporting delay was larger than in the previous years, with less than 31% being reported within 28 days compared to 35% on average for all vaccine doses. This points to an increase in reporting willingness or to lower reporting threshold and to a decrease rather than to an increase in (perceived) severity.

7.1.4 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 [36,37,38,39,41,42,44,45]. 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 [38]. 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 [39]. The number of reports in 2000 was 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 [41]. The small rise in number of reported AEFI in 2001, 2002, 2003 may be partly due to a decrease in underreporting in some regions with a somewhat larger proportion of minor events in the regions with the highest increase in reporting rate, but this certainly cannot explain the total increase in numbers [42]. Some of the increase may be the result of introduction of two new vaccines (aK and MenC). It is argued that a better adherence to the accelerated schedule plays a role in the

increase in age specific collapse reactions in the infants. This latter aspect is studied in 2005 using data from the PEA.
The current increase in numbers is due to a general decrease in underreporting, induced by the adverse publicity. This appears to have affected mainly the more common events like (fierce or prolonged) crying and (very) high fever. These events have an estimated incidence rate of 1 per 100 to 1 per 1000 DPTP-Hib vaccinations (dependent on dose number and or age of vaccination); these estimates are obviously dependent on case definition applied. Fever and crying, how uncomfortable they may be, are not events a passive surveillance system aims at. On the other hand reporting criteria include severe events regardless of assumed causal relation, occurring in the applicable risk window for the specific event and vaccine, one might argue that persistent screaming and very high fever should indeed be reported to the passive surveillance system. Incidence rate estimates for fever and crying are more efficiently studied in active design however, since the frequency is high enough. With lower incidence rates numbers needed for a comfortably precise estimate are much larger, prohibiting regular or frequent surveys among parents. For the more specific (and more complex) major adverse events the performance of the current enhanced surveillance system seems better. Facilitating reporting of selected specific adverse events by the professionals may be more rewarding as well as further exploring data linkage studies for events leading to hospital care in majority of cases.
One of the reporting criteria is events leading to public apprehension. The current enhanced passive surveillance system apparently is very (signal) sensitive in this respect as has been shown by the sharp increase in number of reports and in the number of consultations.
See for further inference on reports of collapse, convulsions and discoloured legs the following subparagraphs under 7.2.
The stable rather even distribution of the reporting rates over the country suggests a satisfactory performance of the passive surveillance system.

7.2 Specific Events

In addition to what is said in the above paragraphs on specific adverse events some specifics will be discussed below.
To get information on incidence rates of some more severe events RIVM has started an active surveillance study in December 2003 aiming at 30-40,000 doses DPTP-Hib. This study focuses at persistent screaming, very high fever and at the more complex events as collapse and convulsion. Also are addressed the use of paracetamol and hospital visits. Some other adverse events have been included for exploring e.g. discoloured legs and urticaria. Results are expected by 1-1-2006.

7.2.1 Persistent screaming

Intensified and continuous inconsolable crying has been an acknowledged adverse reaction for decades. It has been attributed mainly to the pertussis component. Often the definition for this event has a certain length of time included. Most commonly this is 3 hours. But studies differ greatly in this respect. Some supply no definition at all, have no time limits for

duration or focus only on inconsolability. Other studies state time limit of one hour but do not include continuousness in the criteria. It does not need arguing that used case definition is of great influence on the incidence estimates. This is exemplified in a recent article on excessive crying in infants. It is stated that infants cry on average 2 hours a day during the first months of life, with a peak at 6 weeks with 2.5 hours on average. In letters to the editor it has been shown that the incidence varied from 2.0% to 12.7% depending on inclusion criteria [65,66,67,68]. Lately the case definition for persistent crying has been redefined by the Brighton Collaboration, with three levels of fitting [69]. Our existing case definition differs to the Brighton's only with respect to the lower boundary of duration; we include 3 hours and more compared to more than 3 hours. We register the duration however in order to be able to pool or compare results.
The reported 133 cases of persistent screaming (1 per 2500 first doses of DPTP-Hib) is however nowhere near the estimated 1-10 per 1000 children experiencing persistent crying depending on case definition and age involved. As we have stipulated in paragraph 7.1 this is to be expected and of no serious consequence for the safety profile of the RVP. The performed active questionnaire study on the more severe adverse events following DPTP-Hib will address the incidence rate for this particular adverse event. More than before the fear of lasting sequelae of persistent crying was apparent and the wisdom of further vaccinations questioned. Somehow this has entered the public debate implicitly; there are however no, existing or new, indications that this event is linked independently to other severe or lasting conditions.

7.2.2 Very high fever

Fever is a very unspecific symptom of very many medical conditions. It is also an acknowledged adverse event following immunisation. In all pre registration trials this event is covered. The Brighton Collaboration covered this event in the first series of six with stipulations how to report in increment of .5 degrees centigrade (Celsius). Some discussion is still the measurement requirements of fever and the devices used or acceptable [70]. Some national or regional "habits" still cloud the discussion, (i.e is rectal preferable above oral or axillar and are new modern devices acceptable, etceteras). These issues will be addressed later on when evaluating the use of the case definitions over time and place. We have registered events under very high fever only if the event was not part of another disease entity. Altogether 199 events were reported with very high fever involved, of which 118 in the approx one-year-olds. For DPTP-Hib4 this works out to 1 per 3500 vaccinations compared to the estimated rate of 1/100 to 1/1000, a clear underreporting. Not all cases in these estimated rates represent true causality however. Concomitant events with very high fever are rather common at this age. As stipulated before the safety profile of the RVP does not depend on the number of reported events of very high fever. See for more comments under subparagraph 7.2.1.

7.2.3 Collapse reaction

Reports of collapse reactions appear to have truly increased in 2001 with 21% compared to 2000 but have more or less stabilised since then. This year the number of reports following the first vaccinations with DPTP-Hib is again within range. The number of reports of recurrent collapse is higher than before however. The current analysis (in 2005) on this signal will answer this topic and estimate the rate of recurrence since the accelerated schedule. Distribution again over the different doses suggests a strong age effect but also some dose effect since the number of collapse after the first vaccination (nearly) doubled but after the second vaccination is half to three quarter of the number at three months of age before the change in schedule. The effect of different contents in completeness of the event will be studied also in 2005. We will comment on this in our report on collapse reactions (in preparation). The reporting rate of collapse remained more or less the same with only some increase in collapse following the second DPTP-Hib. This might underline that for this event the reporting rate is very much in line with the true incidence rate. The estimate of this remains 1 in 1000-1500 children. We will apply the agreed Brighton case definition on all reports of collapse since 1994 and also compare the yield with 2004 [71].

7.2.4 Discoloured legs

Numbers of reported discoloured legs have increased largely compared to 2003. A substantial part of this is due to inclusion of 49 reports from the active questionnaire survey and also from reports on recurrent discoloured legs (71 multiple reports altogether). Distribution over the different doses remained more or less the same, with some effect of the younger age, also suggesting a stronger dose than age effect, for first time episodes. This is 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. There is no report in international literature and subsequently no other estimate of the incidence rate, nor of the rate of recurrence. The doubling of reports following the first dose warrants further investigation. The number of compound reports with (simultaneous) collapse reaction has also increased compared to previous years. Some of these reports concern very transient, localised or undefined events. 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, e.g discoloured leg syndrome, local reactions or swollen limp. We will look for consensus in the Brighton collaboration for this event and (re) apply a consistent case definition later on the reported events [72,73]. We will look into the event of discoloured legs in the next year, along with the analysis of the active questionnaire survey.

7.2.5 Convulsions and Atypical Attacks

The number of (classic) febrile convulsions following DPTP/Hib and MMR1 vaccinations was somewhat higher than in previous years. This applies both to DPTP-Hib4 and to MMR

and MenC vaccinations. The incidence rate for causally related febrile convulsions (based on assumed coverage data) is 1.5 per 10,000 (1.0-2.1/10,000) some increase compared to 2003 (0.8/10000, c.i. 0.4-1.2). Irrespective of assessed causality for DPTP-Hib4 the rate is 1.9 (c.i. 1.3-2.6) per 10,000 vaccinations compared with 1.3 (0.8-2.1) per 10,000 vaccinations in 2003. This may be random fluctuation as well as some decrease in underreporting. Estimates from more active studies being 1 event in 5000-10,000 vaccinations are still in line with actual reports in the enhanced passive surveillance system [74,75]. This suggests a very satisfactory performance of the system in this respect.
The number of reported atypical attacks was quite substantially higher than the previous year. Numbers have fluctuated considerably however. This is not surprising if one considers this subcategory to be the dustbin of paroxysmal events not otherwise classifiable. We follow the reports in this subgroup with scrutiny but up till now no specific trends or signals have come up. The numbers in this subgroup are (very much) dependent on completeness of information. Thus, in different years transfer to and from other event categories varies. If planning and priorities permit, we plan to look into the phenomenon of atypical attack in more detail. The stable and low number of reports of non-febrile convulsions may reflect non-causality in the first place [75]. Since 1996 numbers vary between 0-6 reports a year, with in the current year 8 reports, all considered coincidental events.

7.2.6 Pervasive Disorders and Retardation

Press allegations about possible causal relation between MMR vaccination and autism dented the confidence of parents in the vaccination programme [76,77]. Despite the fact that based on scientific evidence renowned (groups of) scientists have refuted these alleged associations, especially in the United Kingdom and the Republic of Ireland the vaccination coverage dropped considerably [78,79]. In the current year we have received very few reports on behavioural problems in the autistic spectrum or other a specific problems in mental retardation. Some parents have no real suspicion but have been made insecure, others simply clutch the last straw. In none of the reported cases a causal relation was found, and in some the event preceded the vaccination.
It is to be expected that 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 [80,81]. Those refuting the causal relation of encephalopathy or retardation with pertussis vaccinations have been published earlier. No new signals have emerged from the reports of 2004.

7.2.7 Epilepsy

The number of reports on epilepsy was within the range of the last five years, with comparatively a rather large variation, as is to be expected with such small numbers. In none of the reports causality was assumed. The eight children with non febrile convulsions were all

suspected of underlying epilepsy. In none of them the epilepsy itself was considered caused by the vaccination however. Numbers may reflect to some extent (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 [75]. 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 [59,82]. However, the age at which West syndrome occurs coincides with the vaccination schedule.

7.2.8 Death

This year four children were reported that died some time after immunisations. One child with severe underlying disease dies following the third dose of palivizumab, monoclonal antibodies against RSV infections. This child's report was forwarded to Lareb. The number of reports in this category is in line with expectations considering the background rate. Surprising is however that no reports of death following DPTP-Hib vaccinations were received, in a year full of adverse publicity of alleged severe effects of DPTP-Hib vaccinations.
In none of three remaining children, all with death after MMR and MenC vaccination, causality was considered to be present, after thorough evaluation, with the given vaccinations. Neither was there considered indirect causality, with delay in treatment or aggravation of symptoms because of the vaccination. In one child a full post mortem has not been performed leaving room for uncertainty and speculations. It should be stressed that full post mortem investigations of any child in infancy or at young age is advisable, even if underlying severe conditions are present. This is beneficial both for the case of the affected child, its distressed parents and for the entire population.
Systematic studies and evaluation of the Institute of Medicine have shown infant death to be unrelated to childhood vaccinations [83]. 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.
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.

7.3 Safety Surveillance of the RVP

Safety surveillance of the vaccination programme seems to be of increasing importance [13,14,84,85,86]. The Dutch system has several strong points. Denominators are known, because the PEA registers all administered vaccines on individual level [48,54,58]. The installation of the web-based new central immunisation registry will allow more specific and timely data extracting (Praeventis). The data warehouse tool will make data extraction more efficient. (Praemis). The RVP is embedded in the regular Child Health Care with its near total coverage and programme delivery by a relatively small group of specifically trained professionals. Good professional standards include asking about adverse events at the next clinic visit and before the next dose. The RIVM's (24-hr) central telephone information and consultation service for professionals is a most important and efficient tool in adverse events reporting [87]. It also allows a close watch on risk perception and programme adherence. Reporting in low-level terms with signs and symptoms and not only (assumed) diagnoses allows application of standardised case definitions and stratified analysis if necessary. Validation and supplementation of reporting data from medical records and eye witness case histories is an important aspect of the system resulting in homogeneous event categorisation. The wide reporting criteria allow sensitive signal detection of new adverse events or interactions. Trend analysis is possible. The nominal reports facilitate follow up and some other systematic studies, like nested case-control studies [45,88.] The current enhanced passive surveillance system performs satisfactory (LIBRIS). The strength of the system outweighs the inherent weaknesses. Additional active surveillance studies should supplement the passive system. See for further details the subparagraphs below.

7.3.1 Causality Assessment and Case Definitions

Assessing causal relation is essential in monitoring the safety of the vaccination programme [59,85,89,90,91]. Of course, after vaccination does not mean caused by vaccination. The RIVM expert panel will continue the GR activities of broader scientific assessment of selected cases. Some other countries like Canada (with it's ACCA, Advisory Committee on causality Assessment, since 1994) and the USA have followed suit (CISA, Clinical Immunization Safety Assessment Centers, since 2001) [92] . Five different categories are used for causal relation for the purpose of international comparison. However, different design and criteria for surveillance systems, diagnostic procedures, causality assessment and inconsistent case definitions and case ascertainment hamper international comparison [93]. Also different schedules and/or vaccines and combinations do preclude direct analyses or pooling of data and require cautious interpretation.

The Brighton Collaboration, in which RIVM also participates, aims to arrive at defined standardised case definitions for specific adverse events following immunisations. Use of these case definitions is proposed for both pre-licensure studies and post-registration surveillance [10,91]. Performance of vaccines in comparative pre-registration field trials may differ from experiences in actual use in large unselected populations. Therefore (new) vaccines should be monitored intensely and exactly there where they are in actual use.

7.3.2 Passive Surveillance versus Active Surveillance

The current enhanced passive surveillance system will need to be supplemented by more active monitoring and systematic studies to test generated signals and hypotheses. Problems arising from privacy legislation should be addressed. The introduction of a unique medical personal identifier should facilitate data linkage studies, using hospital databases or other electronic medical files. The centralised immunisation register is an asset towards these goals. The enhanced passive surveillance however, will remain the backbone of safety surveillance. In an EU study in several European countries, including the Netherlands, possibilities for improved safety surveillance of vaccination have been explored (EUsafevac 2001-2003) [94,95,96]. Different Health Care systems and vaccine delivery organisations and logistics, with different legislation, traditions, among other things, but also existing differences in safety surveillance already in place make that no unique recommendation could be made. Stressed is however that vaccination registers are a first requisite [97]. These registers should also qualify for safety surveillance. In the Netherlands the new centralised immunisation database fulfils these criteria.

In Canada the national safety surveillance system is placed at the Public Health Agency of Canada (CAEFISS) to ensure that vaccine safety surveillance with its specific aspects is guaranteed. They have an active surveillance system in place for severe adverse events following immunisation, vaccine failure and (future) vaccine preventable infections (IMPACT, a collaboration of the Canadian Paediatric Society and the Centre for Infectious Diseases). In the USA vaccine safety surveillance is also separate from the drug monitoring system situated at the CDC in collaboration with FDA (VAERS). The vaccine safety data link project (VSD) links immunisation record with medical information in the database of some large Health Maintenance Organisations (HMO) to perform active studies testing signals from the passive system. In the Netherlands the placement of the safety surveillance system at RIVM (LIBRIS) with its expertise should guarantee high quality assessment of the safety of the RVP. The collaboration with Lareb should ensure that European legislation is followed.

In the Netherlands the feasibility of using the Paediatric Surveillance Unit more permanently for active signal testing for specific adverse events should be explored. The performance of the system and the degree of participation and coverage should be guaranteed however. Possibilities of electronic databases of paediatric diagnoses should be explored. For the more severe common adverse events questionnaire survey could be done on a regular bases to test the safety profile of the (new) vaccines or schedules in the programme.

7.3.3 Information and Consultation Service

We hold the telephone service to be an important tool in the safety surveillance of the RVP, both for capture of important adverse events or potential adverse reactions and with regard to the quality of data [87, 98]. This low threshold reporting channel has proven to have great advantage over written report forms not only because of superior possibility of communication, timeliness and supplementation of data. Written reports by regular mail, by fax and by e-mail are also accepted. Reporters prefer however the reporting by telephone as

less time consuming and of advantage because of the possible consultation. For data quality reports received by telephone are superior and efficient since they allow necessary supplementation and validation. The telephone service is also an important tool for adherence to the programme, to promote proper use of contraindications and for guidance of the professionals to ensure adequate vaccination in special circumstances or underlying disorders.
In the current year the telephone service had a sharp increase in calls (close to 15.000). Providers and parents both aired their concern fuelled by the media attention to the safety of the vaccination programme. Much more than in previous years this led to (planned) deferral of the vaccination, after adverse events that do not preclude normal continuation of the programme. Quite some parents apparently chose to buy acellular pertussis vaccine from abroad and also some decided to vaccinate only with vaccines without a pertussis component. How often this occurred or how often later doses have been postponed to 2005 when the acellular pertussis vaccine would be available, is not known (yet).
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 [99,100,101,102, 103]. The RVP communication project of RIVM in close collaboration with other parties has developed fact sheets and web based material for parents in spring 2004. It is planned to add more in depth material for professionals. (www.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. See also the following paragraphs on management of adverse events and risk communication.

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 adverse reactions. Adverse coincidental events are truly chance occurrences however. Sometimes postponement of vaccination might free the vaccine and the vaccination programme from allegations of causing an event or disorder that would inevitably have occurred. But deferral should be avoided as much as possible because it will delay protection of the child.

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 [35,36,37,38,39,41,42,44,45]. 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 [47,49,104,105,106]. 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. The increase in reported recurrence of collapse reactions has not led to reconsidering of abandoned contraindications or to formulation of new precautions. We are currently studying collapse reactions to estimate the rate of recurrence more precisely. Preliminary results show this rate to be approximately 4% (c.i. 2-6%) for the second dose and much lower for the subsequent doses. Applying more strict contraindications will not contribute much to prevention of adverse reactions but will result in a loss of protection [107].

7.4.3 Risk Communication

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

The experiences in 2004 with extreme public media concern about the safety of the vaccines have indeed accentuated the need for timely up to date information. Especially professionals have stressed that they should be informed proactively, not only by news letters but also through specific scientifically referenced fact sheets.

7.4.4 Causality Assessment

Causality assessment is important for surveillance purposes of the vaccines, the vaccination programme and for the individuals concerned [85,89]. Individual continuation of the schedule depends on proper assessment. It is important for the entire population served also, as in quietude and commotion will result in diminished coverage. One should acknowledge genuine adverse reactions and recognise evidently coincidental events both. Careful causality assessment will exonerate the programme from severe but unrelated adverse events. It will also detect new rare adverse reactions and as yet new unrecognised more common side effects. Therefore thorough causality assessment will enhance the safety of the programme.

7.5 Considerations for the Safety Surveillance of the RVP

2004 has shown that the enhanced passive surveillance system picked up signals of increased reports and public apprehension quickly [108]. We discussed implications of these signals already in the first week of January with the Ministry of Health and the directors of the RIVM.

The system performed satisfactorily for events like collapse and convulsions. It's worth to increase the reach of the system not only among the current providers, but especially among pediatricians. This may yield more reports but this also should result in more timely reports. Depending on type of event, supplementation of the system with active surveillance through parental questionnaires or pediatric surveys is necessary.

Possibilities of data linkage must be explored. Shortcomings like 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. Medical data must be validated and contain enough information to apply (internationally) agreed case definitions.

An adequate database system is a prerequisite for this as well. The data put into the system must be of good quality nevertheless, therefore this should get a lot of attention. "Rubbish in rubbish out" also applies to safety surveillance.

Structural feedback to reporters and otherwise involved professionals should be addressed in the new database application. This also serves (expedited) passing on of reports to Lareb and manufacturers.

It was also shown in 2004 that there was great need for timely and up to date safety information. Results from the surveillance system and the inference and implications should be available in comprehensive format, both for professionals as for public. The system should also decisively address adverse publicity and other signals. Proactively scientifically based

fact sheets on severe and rare events may counteract unfounded future allegations. Those fact sheets will help the professionals to deal with correct or inappropriate contraindications.

8 Conclusions and Recommendations

In 2004 the number of reported events increased significantly (56%) due to adverse publicity. This put a strong claim on the safety surveillance and information system. It also showed the necessity of intensive surveillance of adverse events following immunizations of vaccination programmes. The need was felt for up to date and scientifically based information to professionals and public.

We found no new, severe or unexpected adverse events. The increase was mainly due to increase of fever and crying, on which the discussion focussed.

For this type of events periodic surveys are the appropriate tools to check on incidence rates. For more rare severe events like collapse and convulsion the enhanced passive surveillance system performs satisfactorily. For events with clear underreporting the need for different (active) study designs have to be explored, like data-linkage and active surveillance through paediatricians.

The safety surveillance and information system was clearly signal sensitive. Early in 2004 we picked up the unusual number and type of reports and the accompanying public apprehension. The telephone information service played a valuable role in supporting professionals. The quality of this service 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 [109,110].

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 2005;
- maintenance and evaluation of the current passive surveillance system;
- further increasing reporting compliance of child health care providers;
- promoting safety surveillance and information system among paediatricians;
- epidemiology of collapse reactions and follow up, also including the effect of the accelerated schedule;

- descriptive epidemiology and follow up of discoloured leg syndrome;
- 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;
- 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 2141 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 2004

STAATSTOEZICHT OP DE VOLKSGEZONDHEID

INSPECTIE VOOR DE GEZONDHEIDSZORG

Rijksvaccinatieprogramma 2004

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

- 2004: DKTP-Hib (gemengd) + Hep B[1]
- 2003: DKTP-Hib (gemengd) + Hep B[1] + BMR + Men C
- 2000: DTP + aK
- 1995: DTP + BMR

1 Algemeen

1.1 Organisatie

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

1.2 Vaccindistributie

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

1.3 Registratie en verantwoording

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

1.4 Financiële regels

De kosten van de uitvoering van het Rijksvaccinatieprogramma komen ten laste van de 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.

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

1.5 Uitzonderingen

Indien ouders kiezen voor een ander vaccin dan dat door de Minister voor gebruik in het RVP is aangewezen en/of indien ouders kiezen voor toediening van RVP-vaccins buiten de leeftijd of leeftijdsmarges die in de AWBZ-verstrekking zijn aangegeven, vervalt het recht op kosteloze verstrekking en dienen zij zich met hun wensen tot de huisarts te wenden. Voor vaccinaties, gegeven overeenkomstig bovengenoemd Rijksvaccinatieprogramma, doch zonder tussenkomst van de Entadministraties, worden **geen** gratis vaccins ter beschikking gesteld, noch enige vergoeding gegeven.

1.6 Onvolledig gevaccineerden

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

Daarbij gelden de volgende beperkingen:

- Voor de Hib-vaccinaties dat alleen kinderen die geboren zijn vanaf 1 april 1993 voor vaccinatie in aanmerking komen.
- Voor de aK-vaccinatie dat alleen kinderen die geboren zijn vanaf 1 januari 1998 en die de basisserie DKTP hebben voltooid, voor vaccinatie in aanmerking komen.
- Voor de Meningokokken C-vaccinatie dat alleen kinderen die geboren zijn vanaf 1 juni 2001 voor vaccinatie in aanmerking komen.
- Voor de Hepatitis B-vaccinatie dat kinderen 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%), voor vaccinatie in aanmerking komen. Verder komen voor de Hepatitis B-vaccinatie in aanmerking kinderen van HbsAg-positieve moeders (draagsters van het Hepatitis B-virus).

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

1.7 Algemene regels ten aanzien van het toedienen van de vaccins

Het toedienen van RVP-vaccins is een medische handeling. Voor het wel of niet toedienen hiervan en voor het afwijken van de in het schema aangegeven leeftijdsmomenten (zie paragraaf 7) geldt derhalve, dat hiertoe altijd door een arts een indicatie moet zijn gesteld.
Voor alle vaccins in het kader van het Rijksvaccinatieprogramma geldt, dat halvering van de dosering van een vaccin niet is toegestaan. Het effect hiervan op de werkzaamheid is namelijk onbekend, terwijl het niet leidt tot minder bijwerkingen. Ook andere afwijkende doseringen of verdunningen van de vaccins zijn niet toegestaan.
Verder geldt voor alle vaccins, dat deze niet intravasculair toegediend mogen worden.

1.8 Nadere regelingen

Alle nadere regelingen welke met betrekking tot het Rijksvaccinatieprogramma 2004 worden getroffen, vereisen de goedkeuring van de Inspecteur-Generaal voor de Gezondheidszorg.

1.9 Aanvragen extra circulaires

Exemplaren van deze circulaire kunnen worden aangevraagd bij de Inspectie voor de Gezondheidszorg, Postbus 16119, 2500 BC Den Haag, telefoon 070 340 5536 of bij de regionale Entadministratie (zie paragraaf 8).

2 Zuigelingen

Vaccinatieschema

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

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

Separaat toedienen van DKTP- en van Hib-vaccin is niet meer toegestaan in het kader van het RVP. Hierop kunnen zich twee uitzonderingen voordoen:

- Er bestaat een medische contra-indicatie, ter beoordeling aan de indicerend arts, voor het toedienen van of de DKTP- of de Hib-vaccinatie. Het vaccin dat wel geïndiceerd is, kan dan separaat worden toegediend.
- Aan kinderen, die op latere leeftijd Nederland binnenkomen en die in aanmerking komen voor Hib-vaccinatie, maar niet (meer) voor DKTP-vaccinatie, mag Hib-vaccin separaat worden toegediend.

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. Indien DTP wordt toegediend moet de Hib-vaccinatie apart (beide in verschillende ledematen), maar wel simultaan (op dezelfde dag) worden gegeven. DTP-vaccin en Hib-vaccin mogen **nooit** gemengd worden. Er zijn overigens geen absolute contra-indicaties tegen de kinkhoestvaccinatie meer.

- **Hep B (Hepatitis B)**

Voor deze vaccinatie komen uitsluitend twee groepen kinderen in aanmerking:

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

Aan deze kinderen wordt op de leeftijd van **2** en **4** maanden één Hep B-vaccinatie gegeven. De **derde** Hep B-vaccinatie wordt bij voorkeur op de leeftijd van 11 maanden gegeven. Er dient **tenminste een tussenperiode van 6 maanden** in acht te worden genomen tussen de tweede Hep B-vaccinatie en de derde Hep B-vaccinatie.
Dosering: 0,5 ml INTRAMUSCULAIR.

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

De Hep B-vaccinatie wordt simultaan (op dezelfde dag) met de gemengde DKTP-Hib-vaccinatie gegeven, waarbij het Hep B-vaccin en het gemengde DKTP-Hib-vaccin in verschillende ledematen worden toegediend.
Uitstel van de Hep B-vaccinatie is niet toegestaan voor kinderen met een moeder die draagster is van het Hepatitis B-virus (HbsAg-positief). Bij deze kinderen moet de Hep B-vaccinatie te allen tijde uiterlijk op de leeftijd van 2 maanden gestart worden en indien mogelijk nog eerder.
Kinderen van HbsAg-positieve moeders komen tevens in aanmerking voor het toedienen van immunoglobuline direct na de geboorte, maar dit valt buiten het kader van het RVP.

- **BMR (Bof – Mazelen – Rodehond)**

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

- **Men C (Meningokokken C)**

Op de leeftijd van 14 maanden wordt één Men C-vaccinatie gegeven.
Dosering : 0,5 ml INTRAMUSCULAIR.

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

3 Kleuters

Vaccinatieschema

- **DTP (Difterie – Tetanus – Poliomyelitis)**

De in 2000 geboren kinderen worden in 2004 gerevaccineerd met DTP-vaccin. Afhankelijk van de reeds eerder gegeven vaccinaties worden 1, 2 of 3 vaccinaties toegediend.
Dosering: 1 ml INTRAMUSCULAIR.

- **aK (Kinkhoest – acellulair vaccin)**

De in 2000 geboren kinderen worden in 2004 gerevaccineerd met aK-vaccin, maar uitsluitend indien zij al eerder een volledige serie DKTP-vaccinaties hebben ontvangen. Er wordt één aK-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.

4 Schoolkinderen

Vaccinatieschema

- **DTP (Difterie – Tetanus – Poliomyelitis)**

De in 1995 geboren kinderen worden in 2004 gerevaccineerd met DTP-vaccin. Afhankelijk van de reeds eerder gegeven vaccinaties worden 1, 2 of 3 vaccinaties toegediend.
Dosering: 1 ml INTRAMUSCULAIR.

- **BMR (Bof – Mazelen – Rodehond)**

De in 1995 geboren kinderen krijgen in 2004 een BMR-vaccinatie.
Dosering: 0,5 ml SUBCUTAAN.

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

5 Simultane vaccinaties en registratie van partijnummers

Simultane vaccinaties zijn vaccinaties die op dezelfde dag, meestal (vrijwel) gelijktijdig, worden toegediend. Deze toediening dient altijd in verschillende ledematen plaats te vinden.

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

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

6 Bijwerkingen

Na vaccinaties kunnen bijwerkingen optreden. Meestal betreft dit lichte, veelal lokale verschijnselen. Elke bijwerking, zeker de meer ernstige, kan de vaccinatiegraad negatief beïnvloeden. Er wordt dan ook dringend verzocht elke ernstige,

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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 nibris@rivm.nl).

7 Vaccinatieschema per kind

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

8 Entadministraties

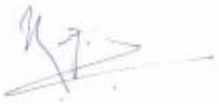
Voor inlichtingen met betrekking tot het Rijksvaccinatieprogramma en over de wijze van uitvoering kan men zich wenden tot de voor de regio betreffende Entadministratie.

Groningen/Friesland/Drenthe
Postbus 4050, 9701 EB Groningen
Telefoon 050 368 6350, Fax 050 312 2733
Email info@stenn.nl
Overijssel/Flevoland
Postbus 43, 7730 AA Ommen
Telefoon 0529 455 717, Fax 0529 455 805
Email info@entorganisatie.nl
Gelderland
Postbus 357, 6800 AJ Arnhem
Telefoon 026 442 9242, Fax 026 443 4999
Email ent@speg.nl
Utrecht/Noord-Holland
Postbus 1097, 3600 BB Maarssen
Telefoon 0346 550 040, Fax 0346 573 795
Email algemeen@entutrecht.nl
Amsterdam
Postbus 2200, 1000 CE Amsterdam
Telefoon 020 555 5460, Fax 020 555 5071
Email jgzent@gggd.amsterdam.nl
Zuid-Holland
Postbus 654, 2700 AR Zoetermeer
Telefoon 079 341 8238, Fax 079 331 5047
Email ent@reazuidholland.nl
Rotterdam
Postbus 70032, 3000 LP Rotterdam
Telefoon 010 433 9518, Fax 010 433 9652
Email ent@ggd.rotterdam.nl
Zeeland
Postbus 53, 4460 AB Goes
Telefoon 0113 224 080, Fax 0113 224 055
Email entadministratie@spkez.nl
Noord-Brabant
Postbus 8220, 5004 GD Tilburg
Telefoon 013 540 0688, Fax 013 540 0086
Email spen@peab.nl
Limburg
Postbus 5148, 6130 PC Sittard
Telefoon 046 452 9910, Fax 046 458 4479
Email info@entadm-limburg.nl

Informatie over algemene, landelijke zaken de Entadministraties betreffend kunt u verkrijgen bij:
LVE (Landelijke Vereniging voor Entadministraties)
Postbus 100, 3980 GB Bunnik
Telefoon 030 299 3187, Fax 030 242 0874
Email lve@entadministraties.nl

Voor achtergrondinformatie over het Rijksvaccinatieprogramma verwijs ik verder naar de website van het ministerie van VWS: www.vaccinatie.minvws.nl en de website van de LVE: www.entadministraties.nl .

Rijksvaccinatieprogramma 2004
tegen: Difterie, Kinkhoest, Tetanus, Poliomyelitis, Bof, Mazelen, Rodehond, Haemophilus influenzae type b, Meningokokken C en Hepatitis B, voor de kinderen geboren in:
- 2004: DKTP-Hib (gemengd) + Hep B[3]
- 2003: DKTP-Hib (gemengd) + Hep B[3] + BMR + Men C
- 2000: DTP + aK
- 1995: DTP + BMR



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

Den Haag, december 2003

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

Appendix 2 Resume Product Information

Vaccines in RVP	Producer	constituents
DKTP-Hib vaccin Diphtheria, 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