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Adverse Events Following Immunisation under the National Vaccination Programme of The Netherlands
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Abstract

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 onwards evaluation was done in close collaboration with the Health Council. Reports are received mainly from child health care professionals primarily by telephone through the vaccine information and advisory service. Further data are obtained, if necessary, from such sources as parents, general practitioners and paediatricians. After supplementation and verification of data a (working) diagnosis is made and causality assessed. This annual report for 2002 presents an overview of all reported AEFIs, with classification according to case definitions and causality. Trend analysis, reporting bias, background rates of specific events and possible pathophysiology of symptoms are discussed. From a total of over 2.5 million vaccinations 1332 AEFIs were reported of which 12 (0.9%) were unclassifiable because of missing information. In 80% (1057) of the classifiable events a possible causal relationship with vaccination was established and in 20% (263) the events were judged as coincidental. Compared to 2001 there were no relevant changes in numbers, causality or severity of reported adverse events.

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Abbreviations

AE	Adverse Event
AEFI	Adverse Event Following Immunisation
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
CBS	Statistics Netherlands
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
GGD	Municipal Public Health Department
GP	General Practitioner, Family physician
GR	Health Council
HepB	Hepatitis B (vaccine)
HBIg	Hepatitis B Immunoglobuline
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
IPV	Inactivated Polio Vaccine
ITP	Idiopathic Thrombocytopaenic Purpura
JGZ	Child Health Care
LAREB	Netherlands Pharmacovigilance Foundation
LTR	Laboratory for Vaccine Preventable Diseases (of RIVM)
MAE	Medical Consultant of PEA
MenC	Meningococcal C infection (vaccine)
MMR	Measles Mumps Rubella vaccine
NSCK	Netherlands Paediatrics Surveillance Unit
NVI	Netherlands Vaccine Institute
PEA	Provincial Immunisation Administration (registry)
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
SVM	Foundation for the Advancement of Public Health and Environmental Protection
TBC	Tuberculosis
WHO	World Health Organisation

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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 gebeurt vanaf 1984 in nauwe samenwerking met de Gezondheidsraad (GR). De telefonische informatiedienst van het RIVM is een belangrijk instrument in dit passieve bewakingssysteem. 95% van de spontane meldingen komt telefonisch binnen, in hoofdzaak vanuit de Jeugdgezondheidszorg (84%). Nadere gegevens van anderen dan de melder, bijvoorbeeld van ouders, huisarts of ziekenhuis worden in circa 72% van de meldingen verkregen. Na aanvulling en verificatie volgt het stellen van een (werk)diagnose en causaliteitbeoordeling door artsen van het RIVM. De beoordeling wordt meestal (94%) telefonisch teruggerapporteerd naar de melder. Schriftelijk verslag, veelal van de ernstiger of gecompliceerdere beelden, wordt naar alle medisch betrokkenen gestuurd. Een speciale commissie van de GR herbeoordeelt door hen geselecteerde meldingen individueel en de geaggregeerde gegevens van het jaarrapport steekproefsgewijs tijdens een jaarlijks werkbezoek aan het RIVM. De GR adviseert de Minister van Volksgezondheid jaarlijks over de veiligheid van het RVP. Het RIVM jaarrapport bevat alle binnengekomen meldingen in een kalenderjaar.
Dit is het negende jaarrapport.
In 2002 zijn 1332 meldingen binnengekomen, betreffende 1249 kinderen, op een totaal van ruim 2,5 miljoen vaccinaties per jaar. 12 meldingen (0,9%) waren niet te beoordelen wegens het ontbreken van informatie. 80% (1057) van de meldingen werd als bijwerking beoordeeld met een mogelijk, waarschijnlijk of zeker causaal verband. Een toevallige samenloop werd aangenomen in 20% (263) van de meldingen.
Van de mildere, zogenaamde “minor”, algemene, huid- of lokale verschijnselen (618) werden 432 (71%) meldingen als mogelijke bijwerking uitgeboekt in 2002, met zeven gevallen niet te beoordelen.
De andere zogenaamde “major” postvaccinale gebeurtenissen (gerubriceerd onder convulsies, collaps, verkleurde benen, “ziek-major”, “lokaal-major”, een enkel huidverschijnsel, persistent screaming, encefalopathie en de sterfgevallen) werden 714 keer gemeld en in 88% (625) beoordeeld als mogelijke bijwerking met vijf meldingen niet te beoordelen. Verkleurde benen (in 1995 voor het eerst afgesplitst van de huidverschijnselen) werden 137 keer gemeld, met op zes na in alle gevallen een mogelijke causale relatie.
Collaps, waaronder ook atypische en onvolledige episodes, werd 270 maal vastgesteld, met in zes gevallen geen oorzakelijk verband. Daarnaast enkele keren breath-holding-spells (8) en flauwvallen (19) in oudere kinderen (twee keer zonder oorzakelijk verband geacht). In 2002 werden 45 convulsies gemeld, in op twee na alle gevallen bij koorts. Bij 38 gevallen (86%) werd de convulsie als mogelijke bijwerking beoordeeld (met drie meldingen niet te beoordelen). De 41 atypische aanvallen hadden in 68% (26) een mogelijk causaal verband. Epilepsie (5) werd in alle gevallen niet als bijwerking beoordeeld, maar als coïncidentie. Persistent screaming (aanhoudend krijsen$\geq$3 uur) (46) werd in op een na alle gevallen gezien

als bijwerking. Koorts van ≥40,5°C was de werkdiagnose bij 59 kinderen uit de “ziek-major” groep, op zes na allemaal beschouwd als mogelijke bijwerking en één keer als niet te beoordelen. Van de 36 andere beelden uit de “ziek major” groep was er 22 keer een mogelijk causaal verband. Dit betrof myocloniëen / rillingen (2), vaccinitis (6), maagdarmstoornis (2), rode urine (2), en extreem vermijdingsgedrag (1), in alle gevallen met ook zeer hoge koorts (≥40.5^{o}C). Daarnaast nog ITP (6), apneu/saturatiedaling (1), en ontregeling van een (mogelijke) stofwisselingsziekte (2). De overige 31 meldingen waren coïncidentieel. Er waren acht abcessen, waarvan twee kweken positief voor B-hemolytische streptokokken groep A waren en een kweek negatief bleek. Bij de andere kinderen zijn geen kweken afgenomen. Er waren nog 14 anderszins heftige lokale reacties. Een kind met een “major” huidaandoening bleek ichthyosis te hebben, hetgeen ongerelateerd is aan de vaccinaties.
Er zijn geen kinderen met encefalopathie gemeld in 2002.
De acht sterfgevallen die in 2002 zijn gemeld, zijn alle na uitgebreide evaluatie als toevallige samenloop beoordeeld, hoewel niet in alle gevallen een doodsoorzaak kon worden vastgesteld. Bij op twee na alle kinderen was het tijdsinterval van overlijden en vaccinatie veel te ruim. Die twee kinderen die overleden kort na de vaccinatie hadden beiden een zeer ernstige, op termijn dodelijke aandoening. In deze gevallen kan de stress van de vaccinatie, zoals elke andere lichamelijke belasting mede een rol hebben gespeeld bij het moment van overlijden; bij één van die kinderen is zelfs dat minder waarschijnlijk.
De meeste meldingen betroffen simultane DKTP en Hib vaccinaties (1000). BMR was betrokken in 188 van de meldingen, waarvan 55 maal gecombineerd met andere vaccins.
In 60% was er een mogelijke causale relatie met de BMR. Voor de andere vaccin(combinatie)s was dit percentage 80%.
Vergeleken met 2001 was het aantal meldingen hetzelfde. Wel was er in de verdeling over de ziektecategoriëen een verklaarbare invloed van de twee nieuwe vaccins in het Rijksvaccinatieprogramma. De meldingen over aK en over menC gaven geen aanleiding tot zorg. Los hiervan waren er geen klinisch relevante verschillen in aantal, ernst en causaliteit van de meldingen, vergeleken met 2001. Het totaal aantal mogelijke bijwerkingen moet in relatie gezien worden met het grote aantal verrichte vaccinaties, met meer dan 2,5 miljoen prikken en bijna 7 miljoen vaccincomponenten. De grote gezondheidwinst die de vaccinaties van het RVP betekenen, 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 onwards evaluation is done in close collaboration with the Health Council (GR). The 24h-telephone service for reporting and consultation is an important tool for this passive enhanced surveillance system. 95% of reports come in by telephone, in majority from Child Health Clinic staff (84%). Parents, GP's and/or hospital provided additional data on request (72% of cases). RIVM makes a (working) diagnosis and assesses causality after supplementation and verification of data. The assessment is communicated to the reporting party usually by phone (94%). Written assessments, in case of more serious and complicated events, are sent to all medical professionals involved. A committee of GR reassesses a mutually agreed subset of the latter cases and the aggregated results of the others annually, and conducts cross checks during an audit visit. The GR advises the Minister of Health annually on the safety of the vaccination programme. RIVM reports fully, over all incoming reports in a calendar year since 1994. This is the ninth annual report.

In 2002, on a total of over 2.5 million vaccinations, 1332 AEFI were submitted, concerning 1249 children. Of these only 12 (0.9%) were not classifiable because of missing information. 80% (1057) of classifiable events were judged to be possibly, probably or definitely causally related with the vaccination and 20% (263) of the events were coincidental.

So-called "minor" local, skin or systemic events were registered in 618 cases of which 432 (71%) were classified as possible adverse reactions in 2002.

The other so-called "major" adverse events (categorised under convulsions, collapse, discoloured legs, persistent screaming, general major-illness and death with inclusion of some skin and local reactions) occurred in 714 cases of which 88% (625) were possible adverse reactions. Discoloured legs were reported 137 times with a causal relation more or less likely in all but six cases. Collapse, including atypical and incomplete episodes, was diagnosed

270 times, in only six cases without causal relation. Eight times Breath Holding Spells were reported and 19 times fainting in older children, twice without causal inference. Convulsions were diagnosed in 45 cases, in all but two with fever. In 38 cases (86%) (50) inferred causality and three cases were non-classifiable. 41 Events were considered atypical attacks, of which 68% (26) with a possible causal relation. Epilepsy (5) was considered not causally related with the vaccinations. All of the 46 reported cases of persistent screaming were considered adverse reactions.

Fever $\geq$40.5°C was the working diagnosis in 59 cases of the major-illness group, in all but six with inferred causality. Of the other 36 major-illness cases 22 had a possible causal relation: myoclonics/chills (2), "vaccinitis" (6), gastro-enteritis (2), red urine (2) and extreme "avoidance-behaviour" (1) with in all cases also very high fever ($\geq$40.5^{o}C). Furthermore ITP (6), apnoea/decreased saturation (1) and derangement of possible metabolic disorder (2). The

other 31 cases were considered to be unrelated. There were eight abscesses, with two cultures positive for StrepA and one culture negative. 14 other “major” local reactions were reported One child with “major”skin condition appeared to have ichthyosis, unrelated to vaccination. No cases of encephalopathy were reported in 2002.
In 2002 all eight reported deaths were considered chance occurrences.after thorough assessment, with no definite other causes established in some however. In all but two cases the time interval with the vaccination was far outside the risk window for the vaccines concerned. The two children that died shortly after vaccination had an underlying deadly condition (malformation of the heart and metabolic disease). The stress of the vaccination, like all other physical excertion, could have contributed to the time of of death in one child; in the other even that was considered very unlikely.
Most frequently reports involved simultaneous DPTP and Hib vaccinations (1000). MMR was involved 188 times, 55 times with simultaneous other vaccines. In 60% of cases there was a possible causal relation with MMR. For the other vaccine combinations this percentage was 80%. Compared to 2001 the number of reports was equal. In the distribution of the reports over the different vaccines there was some explanable influence of the two newly introduced vaccines. The reports on aK and MenC were no cause for concern. Apart from this there were no clinically relevant changes in numbers, nature, severity and causality compared to 2001.
The total of 1332 reports should be weighted against the large number of vaccines administered, with over 2.5 million vaccinations and nearly 7 million 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 is evaluated in close collaboration with the Health Council (GR). The annual reports of GR limit themselves to advising the Minister of Health on the safety issues of the RVP. By their nature they do not permit comparing rates and types of adverse events between different vaccines, schedules or vaccine lots. The introduction of a vaccine against Haemophilus influenzae type b (Hib) coincided with a change in the procedure of registration and assessment of AEFI by RIVM in 1993. The annual reports on adverse events by RIVM 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 2002 report contains a description of the procedures for soliciting notifications, verification of symptoms, diagnosis according to case definitions, and causality assessment. It includes a detailed description of the background, organisation and procedures of the National Vaccination Programme and the embedding in the Child Health Care System (JGZ).

We will discuss some specific adverse events and their relation to the vaccination. Special attention will be given to underreporting, to prevention of adverse events and contra-indications, to trends or other signals. Notifications were followed with special attention because of changes previously noted in some age-specific adverse events judged to be the result of the accelerated schedule and better adherence to it in 2000 and 2001. The new booster vaccination for the 4-year olds with acellular pertussis was followed with particular interest. This year was marked also by the national MenC-campaign, with increasing numbers of children vaccinated before, by parental choice. MenC vaccination is included in the programme for the one-year-olds from September 2002. These children are included in this report, while AEFI in the MenC-campaign will be reported separately. The safety surveillance system has been repositioned within RIVM as off January 2002, ensuring independent surveillance from vaccine manufacturers. This process will continue in 2003 with the splitting off of the vaccine department as Netherlands Vaccine Institute (NVI). NVI, and no longer RIVM, is marketing authorisation holder for several former RIVM vaccines used in the programme. The GR has been reconsidering its role in the safety evaluation of the vaccination programme in the light of this reorganisation. For the year under report these developments have not influenced procedures. This RIVM report on adverse events is only issued in English. A five-year overview in Dutch is in preparation.

2 Post Marketing Surveillance

Post marketing surveillance (PMS) consists of all actions towards better knowledge and understanding of (adverse) effects of vaccines beyond the pre-registration research. This is particularly relevant for the identification of rare as well as late adverse reactions, as their rate of occurrence can only be estimated after vaccine use in large populations over a long time [1]. Insight in overdose consequences or use in special groups or circumstances and interactions can be gained only through PMS. Moreover, actual field effectiveness of many or most vaccines and vaccination programmes can only be determined after use over a long time in unselected populations and circumstances. The surveillance of the RVP is an acknowledged task of the National Institute of Public Health and Environment (RIVM): the safety surveillance by the Laboratory for Vaccine-Preventable diseases (LTR) and the surveillance of effectiveness by the Centre for Infectious Disease Epidemiology (CIE) [2].
Requirements for Post Marketing Surveillance of adverse events have been stipulated in Dutch and European guidelines and legislation [3,4] . The World Health Organisation (WHO) advises on monitoring of adverse events following immunisations (AEFI) against the target diseases of the Expanded Programme on Immunisation (EPI) and on implementation of safety surveillance in the monitoring of immunisation programmes [5]. The WHO keeps a register of adverse reactions as part of the global drug-monitoring programme [6]. Currently there are several international projects to achieve increased quality of safety surveillance and to establish a register specifically for vaccines and vaccination programmes [7,8,9].
Close evaluation of the safety of vaccines is of special importance for maintaining public confidence in the vaccination programme as well as maintaining motivation and confidence of the health care providers. With the successful prevention of the target diseases, the perceived side effects of vaccines gain in importance [10,11]. Not only true side effects but also events with only temporal association with vaccination may jeopardise uptake of the vaccination programme [12]. This has been exemplified in Sweden, in the United Kingdom and in Japan in the seventies and eighties of the last century. Commotion about assumed neurological side effects caused a steep decline in vaccination coverage of pertussis vaccine and resulted in a subsequent rise of pertussis incidence with dozens of deaths and hundreds of children with severe and lasting sequelae of pertussis infection [13]. The diphtheria epidemics in Eastern Europe are also result of anxiety about safety of vaccination (procedures) [14]. But also recently concern about safety rather than actual causal associations caused cessation of the hepatitis B programme in France [15,16]. Even at this moment the uptake of MMR in the UK and the Republic of Ireland is very much under pressure because of unfounded allegations about association of the vaccine with autism and inflammatory bowel disease [10,17,18,19,2021,22,23,24,25]. Subsequent (local) measles epidemics have occurred [26,27,28,29].
To counteract similar (unfounded) disquiet in The Netherlands, RIVM has looked for a broader framework of safety surveillance, with a more scientific approach and independent reassessment. This led to the installation of a permanent committee of the Health Council (GR) in 1984. This committee reassessed the more severe events presented by RIVM. The

repositioning of the safety surveillance within RIVM led to reconsideration of this GR role. For the year under report this has not resulted in a change of procedures. The GR advises the Minister of Health on the safety of the Vaccination Programme with annual reports [30,31]. Since the GR reports have no direct reference to year of notification or vaccination and contain a selection of reported adverse events they cannot be used for analysis of trends or patterns in reporting of events nor for comparison of vaccines, lots or schedules. The annual reports of RIVM on adverse events aim to contribute to these goals, however, and may lead to specific follow up and systematic study of selected adverse events [32,33,34,35,36,37,38,39,40]. We hope this will lead to better understanding of pathogenesis and risk factors of specific adverse reactions. In turn, this may lead to changes in the vaccine or vaccination procedures or schedules and adjustment of precautions and contra-indications and improved management of adverse events. These reports may also serve for the purpose of public accountability for the safety of the programme.[41]

3 The Netherlands Vaccination Programme

3.1 Vaccines and Schedule

In the Netherlands mass vaccinations of children were undertaken from 1952 onwards, with institution of the National Vaccination Programme (RVP) in 1957. From the start all vaccinations covered, were free of charge and have never been mandatory. Although a law existed on smallpox vaccinations, this law has never been enforced. With the eradication of smallpox vaccinations were abandoned and this law was revoked in 1978 [42,43]. At first mono-vaccines against diphtheria, pertussis and tetanus were used and the combined DPT vaccine since 1957. After the polio epidemic in 1956, vaccination against poliomyelitis was added. From 1962 onwards the combined DPTP vaccine, with an enhanced polio component (1978), is in use for vaccination of infants and young children and DTP(olio) for revaccination of older children. Rubella vaccination for 11 year old girls was added in 1974 and measles vaccination for 14 months old children in 1976. In 1987 the combined measles, mumps and rubella (MMR) vaccine replaced the mono-vaccines in a two-dose schedule for all children (14 months and 9 years). Mid 1993 vaccination against (invasive) infection with Haemophilus influenzae type b (Hib) was added for children born after April 1st 1993. The actual RVP schedule of 2002 is included in box 1 (appendix 1).
From March 1999 onwards vaccinations start at an earlier age in the programme, at two months of age in stead of three. This was decided upon to achieve protection as early as possible for the youngest, most vulnerable children, because of the resurgence of pertussis in the Netherlands. The aim is to have given all children the third dose at five months of age. It was shown that with the prior schedule about one quart of children had not finished their primary series before six months of age [44]. 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 [45].
From September 2002 onwards MenC vaccine is also included in the programme following a national MenC campaign for all children 1-19 years.

Box 1. Schedule of the National Vaccination Programme of the Netherlands in 2002

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

*menC for children born from 1 June 2001

DPTP, DTP and MMR are produced by SVM/RIVM (currently NVI- Netherlands Vaccine Institute); Hib (PRP-T) vaccine is produced by SVM/Pasteur-Merieux but registered in special presentation form by RIVM (currently NVI)(see appendix 2-5). aK is produced and registered by GSK, but filling final bulk into vials is done by SVM (appendix 6). MenC

vaccine is from Baxter (appendix7). BCG vaccination is not included in the RVP. Vaccination is however offered to children with higher risk of acquiring tuberculosis when travelling to or staying in countries with a high prevalence, free of charge. Usually BCG vaccination takes place in the second half-year of life [42]. Hepatitis B vaccination (HepB) is available for children of HBsAg positive mothers. This vaccination is given, following HBIg administration at birth, in a four adult-dose schedule at the ages of 2, 3, 4 and 11 months during the regular Child Health Clinic visits, simultaneous with DPTP and Hib. In Amsterdam, with a higher prevalence of HBV carriers, a different schedule and delivery system is operational. 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 [42]. For the RVP this age limit is 13 years.
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.
Because of some local epidemics of menC infections a small regional vaccination campaign has been organised in 2001 and early 2002. The vaccines were supplied by the government and were free of charge in the designated area [46]. Public anxiety resulted in over 400.000 administered doses of conjugated MenC vaccines, including infants who received up to three doses before the campaign started in June 2002.

3.2 Vaccine Distribution and Registration

Vaccines for the RVP are supplied by SVM/RIVM and are kept in depot at a regional level at the Provincial Immunisation Administration (PEA) [42,47]. The PEA is responsible for further distribution to the providers. It also has the task to implement and monitor cold chain procedures at the Child Health Clinics (CB) and Municipal Health Care Service (GGD). The Medical Consultant of the PEA (MAE) promotes and guards programme adherence.
The databases of the PEA contain name, sex, address and birth date of all children up till 13 years of age. The databases are linked with the municipal population registers and are updated regularly or on line, for birth, death and migration.
The PEA sends an invitation for vaccination, with a vaccination-registration document and information, to the parents of every child in the second month of life or after immigration. A bar coded card for every scheduled vaccine dose is included. These cards are to be returned to the PEA by the provider after the vaccine is administered. Duplicate cards are available at the vaccination settings. Returned cards are also used for remuneration of the costs of vaccinating (approx. 5 Euro per vaccine) to the health care organisation. All administered vaccinations are entered in the databases of the PEA on individual level; the PEA sends reminders to the child’s address if necessary. The databases serve also the providers who can check the vaccination status of individual children, or of the population they serve. The data of the PEA follow the child when it moves from one place to another. Currently a new national web based database is being built with improvements in functionalities.
The PEA databases also contain results of heel prick tests and of prenatal hepatitis B screening and subsequent vaccinations and results of prenatal tests on blood group incompatibilities and irregular antibodies.

3.3 Child Health Care System

The Child Health Care system (JGZ) aims to enrol all children living in the Netherlands. Child Health Care in the Netherlands is programmatic, following national guidelines with emphasis on age-specific items and uniform registration on the patient charts, up till the age of 18 years [43]. Up till four years of age (Pre School) children attend the Child Health Clinic (CB) regularly. At school entry the Municipal Health Care Service (GGD) takes over. From then on the Child Health Care gets a more population-based approach, with special attention to risk groups and fewer individual check-ups.

The first contact with the family usually occurs less than a week after birth when a nurse visits the home for the heel prick test on phenylketonuria, congenital hypothyroidism and adrenogenital syndrome (PKU/CHT/AGS). At a special home visit approximately two weeks after birth, parents get information on Child Health and an invitation for the first CB visit at one month of age. The nurse may make additional house calls.

Up till 15 months of age about ten CB visits take place during which physical check-ups are performed. These include full medical history and growth and developmental screening at appropriate ages and tests of vision and hearing. Weight, height and head circumferences are recorded on growth charts. Validated test forms are used for developmental follow up. Data on physical examination are also recorded in a standardised form. Parents get advice on food and supplements and information about behaviour, safety issues and upbringing. Interval between visits gets larger as age increases, from four weeks to three months up till the age of 15 months and after that with increasing intervals of three, six and nine months up till the age of four years. The child is seen depending on age specific problems alternating by a nurse or a physician specially trained in Child Health. On individual basis this schedule may be adjusted, and the nurse may make house calls.

The RVP is fully embedded in the Child Health Care system and vaccinations are given during the routine visits. Good professional standards include asking explicitly after adverse events following vaccination at the next visit and before administration of the next dose. The four-year booster shot with DTP and aK is usually given at the last CB visit, before school entrance. Booster vaccination with DTP and MMR at nine years of age is organised in mass vaccination settings, with a possibility for catch up till the age of 13 years. For refugees and asylum seekers the programme covers vaccination up till 19 years of age.

Attendance of Child Health Clinics is very high, up to 99% and vaccination coverage for DPTP/Hib is over 97% with a slightly lower uptake for MMR of 95% [48,49]. (Accurate numbers on birth cohorts 2000, 2001 and 2002 have not been released by IGZ).

3.4 Safety Surveillance

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

The annually distributed vaccination programme (appendix 1) by the Inspectorate of Health Care (IGZ) encourages Health Care providers to report adverse events to RIVM, giving address, telephone number, fax number and email address. Most municipal and regional Child Health organisations, which provide the vast majority of vaccinations, have explicit guidelines for notifying AE to RIVM. The national guideline book on the RVP with background, execution and procedures contains a (RIVM written) chapter on possible side effects and gives ample information on notification procedures [42]. RIVM promotes reporting through information, education and publications, and by contributing to refresher courses for Child Health Clinic staff. General Practitioners and Paediatricians are informed at symposia and during their training. Feedback to the reporter of AE and other involved professionals has been an important tool in keeping the reporting rate at high levels.
Severe symptoms irrespective of medical intervention and irrespective of assumed causality are to be reported. Furthermore peculiar, uncommon or unexpected events, and events that give rise to apprehension in parents and providers or to adverse publicity are also reportable. Events resulting in deferral or cessation of further vaccinations are considered as serious and therefore should be reported as well (see box 2). Vaccine failures may result from programmatic errors and professionals are therefore invited to report those as well.

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

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

All notifications are accepted, registered and assessed by RIVM, irrespective of nature and severity of symptoms, diagnoses or time interval. No discrimination is made for official reports or consultations regarding adverse events. After receipt of a notification, a physician of RIVM reviews the information. Data are verified and the need for additional information is established. Additional information may be obtained from clinic staff, parents, general practitioners and hospital. Also data from the PEA are collected. Upon verification of symptoms and completion of data a (working) diagnosis is made. Interval with the vaccination and duration of the event is established and causality assessed. The feedback includes a description of verified symptoms, diagnosis and causality assessment by RIVM, and advice on subsequent vaccinations. See for detailed description on procedures chapter 5. Since 1984 the Health Council (GR) re-evaluates reported AE on the basis of formal detailed written assessments by RIVM. These written assessments include the more serious reported events. Criteria for selection of the cases to be presented to GR have been mutually accepted. The other reports are cross-checked sample wise by GR. Since 1994, for reasons specified in chapter 2, RIVM publishes annual reports on adverse events. Repositioning of the safety surveillance system in RIVM in 2002, the reorganisation of the vaccine department to the separate Netherlands Vaccine Institute in 2003 and the changing role of GR in 2003 did not lead to changing procedures for 2002. For further details see paragraph 5.7.

4 Materials

4.1 Post Vaccination Events

Events following immunisations do not necessarily have causal relation with vaccination and some have temporal association only and are in fact merely coincidental [10,11,47]. 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) [50,51,33,34].

Box 3. Origin / Subdivision of adverse events by mechanism

a- Vaccine or vaccination intrinsic reactions	are caused by vaccine constituents or by vaccination procedures; examples are fever, local inflammation and crying. Collapse reaction and persistent screaming, occur less frequently and these maybe due to a special susceptibility in certain children.
b- Vaccine or vaccination potentiated events	are brought about in children with a special predisposition or risk factor. For instance, febrile convulsions.
c- Programmatic errors	are due to faulty procedures; for example subcutaneous administration of absorbed vaccines or non-sterile materials. Also too deep administration of BCG leading to abscess. Loss of effectiveness due to faulty procedures may also be seen as adverse event.
d- Chance occurrences or coincidental events	have temporal relationship with the vaccination but no causal relation. These events are of course most variable and tend to be age-specific common events.

4.2 Notifications

All incoming information on adverse events following immunisations (AEFI) under RVP, whether reports or requests for consultation about cases are regarded as notifications. All notifications are recorded on an individual level. For notifying and information a (24-hr) telephone service is available. This permanent availability with instant consultation and advice makes this notification channel direct, easily accessible and fast, resulting in high

quality of data. Notifications are also received by letter, form or fax or email. For further details see paragraphs 3.3 and 3.4 and chapter 5 on methods.
Notifications can be subdivided in *single, multiple* and *compound* reports (see box 4). Most reports concern events following just one vaccination date. These are filed as *single* reports. If the notification concerns more than one distinct event with severe or peculiar symptoms, classification occurs for each event separately (see also paragraph 5.5). These reports are termed *compound*. If the notification is about different vaccination dates, the report is classified under the most appropriate vaccination date, as single if the events concerned consist of only minor local or systemic symptoms. If however there are severe or peculiar symptoms following different dates of vaccinations then the report is *multiple* and each date is booked separately in the relevant categories. If notifications on different vaccinations of the same child are time spaced the events are treated as distinct reports irrespective of nature and severity of symptoms: this is also a multiple report. Notifications concern just one person with very few exceptions. In case of *cluster* notifications special procedures are followed because of the potential of signal/hazard detection. If assessed as non-important, minor symptoms or unrelated minor events, cluster notifications are booked as one single report. In case of severe events the original cluster notification will, after follow-up, be booked as separate reports and are thus booked as several single, multiple or compound reports.

Box 4. Subdivision of notifications of adverse events following vaccinations

single reports	concern one vaccination date have only minor symptoms and/or one distinct severe event
compound reports	concern one vaccination date have more than one distinct severe event
multiple reports	concern more than one vaccination date have one or more distinct severe event following each date or are notified separately for each date
cluster reports single, multiple or compound	group of notifications on one vaccination date and/or one set of vaccines or badges or one age group or one provider or area

4.3 Reporters and Information Sources

The first person to notify RIVM about an adverse event is considered to be the reporter. All others contacted are “informers”.

5 Methods

5.1 Analysis

The processing and evaluation of notifications of adverse events is directed by a standard operating procedure (SOP 12 N-GCP-08). A physician reviews every incoming notification. The data are verified and the need for additional information is determined. A (working) diagnosis is made on the basis of the signs and symptoms, with assessment of the severity, duration and time interval. Causality is assessed on the basis of the type of vaccine, time-interval and presumed pathophysiological mechanism of symptoms and alternative or other plausible causes of the event. The reporter is informed on the likelihood of a causal relation between vaccination and event and given advice on subsequent vaccinations. Usually this is covered in the reporting telephone call or in a later feedback call. A formal written assessment is only made of selected severe events or “alarming” less severe events and sent to all involved physicians. Anonymised copies of these written assessments are sent to the medical consultant of the PEA (MAE). These documents constitute the main source materials for reassessment by the committee of the GR and their subsequent annual advice to the Minister of Health. For further details see the following paragraphs of this chapter. The change in the positioning of the safety surveillance within RIVM and the splitting off of the vaccine department with subsequent change in role of GR did not affect the procedures in the year under report (2002).

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. This interview is mostly taken by telephone and very rarely nowadays a physician of RIVM visits parents at home or at the clinic.

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 in use 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, the case physicians of RIVM discuss the case in periodic clinical conferences. Minor difficulties in assessment may lead to ad hoc consultations and discussions to arrive at consensus.

5.4 Causality Assessment

Once it is clear what exactly happened and when, and predisposing factors and underlying disease and circumstances have been established, causality will be assessed. This requires adequate knowledge of epidemiology, child health, immunology, vaccinology, aetiology and differential diagnoses in paediatrics.

Box 5. Points of consideration in appraisals of causality of AEFI

- Diagnosis with severity and duration.
- time interval
- biologic plausibility
- specificity of symptoms
- indications of other causes
- proof of vaccine causation
- underlying illness or concomitant health problems

The nature of the vaccine and its constituents determine which side effects it may have and after how much time they occur. For different (nature of) side effects different time limits/risk windows may be applied. Causal relation will then be appraised on the basis of a checklist, resulting in an indication of the probability/likelihood that the vaccine is indeed the cause of the event. This list is not (to be) used as an algorithm although there are rules and limits for each point of consideration (see box 5).
After establishing to what extent the vaccine or vaccination has contributed to the event, its causality will be classified under one of the five listed different categories (box 6).
Certain (conclusive, convincing, definite), if the vaccine is proven to be the cause or if other causes are ruled out definitely; there should be a high specificity of the symptoms and a fitting interval. *Probable* causal relation, if there are no signs of other causes, but a fitting interval and a satisfactory biologic plausibility of vaccine/vaccination as cause of the event. If, however, there are other possible causes or the time interval is only just outside of the acceptable limits or symptoms are rather unspecific the causal relation is classified as *possible*. If a certain, probable or possible causal relation is established, the event is classified as adverse reaction or side effect.

Box 6. Criteria for causality categorisation of AEFI

1-Certain	involvement of vaccine vaccination is conclusive through laboratory proof or mono-specificity of the symptoms and a proper time interval
2-Probable	involvement of the vaccine is acceptable with high biologic plausibility and fitting interval without indication of other causes
3-Possible	involvement of the vaccine is conceivable, because of the interval and the biologic plausibility but other cause are as well plausible/possible
4-Improbable	other causes are established or plausible with the given interval and diagnosis
5-Unclassifiable	the data are insufficient for diagnosis and/or causality assessment

If causal relation is regarded as (highly) *improbable*, there is only a temporal relation or a definite other cause for the symptoms; the event is then regarded as coincidental. 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 considered as well, to what extend the vaccine or vaccination has contributed to the event and how. This is especially important in case faulty procedures are involved or in case individual risk factors exist. This may have implications for management of side effects or contraindications. See also paragraph 4.1 and box 3.
By design of the RVP most vaccinations contain multiple antigens and single mono-vaccines are rarely administered. Therefore, even in case of assumed causality, attribution of the adverse events to a specific vaccine component or antigen may be difficult if not impossible. Sometimes, with simultaneous administration of a dead and a live vaccine, attribution may be possible because of the different time intervals involved.

5.5 Event Categories

After assessment, all adverse events are classified under one of the ten different categories listed and clarified below. Some categories are subdivided in minor and major according to the severity of symptoms. Discoloured legs are a separate category for the purpose of aggregated analysis from 1995 onwards. Formerly these events were either classified under skin symptoms or under local reactions (see also box 7). For classification case definitions are used. Historically adverse events are subdivided in minor and major events. Major is not the same as medically serious or severe, but this group does contain the severe events. Definitions for Serious Adverse Events (SAE) by EMEA and ICH differ from the criteria for major in this report.

- Local (inflammatory) symptoms: consist of inflammation 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 will also cases of abscess or erysipelas. If there are accompanying systemic symptoms, the event is only booked under this category if local symptoms prevail or are considered major.
- General illness: includes all events that cannot be specifically categorised in the other event categories. For instance fever, respiratory or gastric-intestinal symptoms, crying, irritability, change in sleeping pattern or feeding behaviour, upper airway symptoms, rash illness, etceteras, fall under this category. Mild or moderate symptoms are listed under minor general illness, severe symptoms under major general illness. Hospitalisation per se does not preclude uptake in the minor category. Fever of 40.5°C and over is listed, by consent, as major general illness, except if associated with febrile convulsion or as part of another specific event. Prolonged mild or moderate fever is considered minor illness.
- Persistent screaming: (sudden) screaming, non-consolable and lasting for three hours or more, without one of the other specific diagnostic groups being applicable. This considered a major event.
- General skin symptoms: skin symptoms that are not general (rash) illness and not considered extensions of a local reaction fall in this category. Like exanthema or other

rashes as erythaema, urticaria, that are not restricted to the injection site. Circumscript lesions distant from the injection site are included and the harlequin syndrome is booked under skin symptoms as well. Some mild systemic symptoms may be present. Subdivision is made according to severity in minor and major if applicable.

- Discoloured legs: symptoms are diffuse or patchy discoloration of the leg(s) and/or leg petechiae, with or without swelling. Extensive local reactions are not included in this category. Discoloured leg is a separate category from 1995 onwards. By consent this is considered a major adverse event.
- Faints: Collapse reactions (HHE, hypotonic hyporesponsive episode), a sudden pallor, loss of consciousness and loss of muscle tone are included unless these symptoms are explicable as post-ictal state or part of another disease entity. If symptoms are incomplete or atypical this is added as an annotation. In collapse following fierce crying that suddenly stops with or without the clear-cut breath holding phase, specific annotation will be made too. In case of classical breath holding spell with no or very short white phase this event will be listed under faints as a separate group. Fainting in older children is listed as a separate group within this category also. Just pallor or apathy or prolonged sleeping or limpness only is not considered collapse reaction.
- Fits: Convulsions are all episodes with tonic and/or clonic muscle spasms and loss of consciousness. There is discrimination by body temperature in non-febrile and febrile convulsions. If fever is $\geq$38.5°C it is booked as febrile convulsion unless the convulsion is symptomatic for meningitis or for other illness. Febrile seizures of more than 15 minutes or asymmetrical or recurring within 24 hours are complex as opposed to simple (classic). Definite epileptic fits or epilepsy are included in this category also. Unspecifiable atypical attacks are a separate group under fits. These are paroxysmal occurrences without the specific criteria for collapse or convulsions or could not be diagnosed definitely as chills or myoclonics e.g. Nocturnal myoclonics are not included, neither are episodes of irritability, jitteriness or chills; these are grouped under general illness.
- Encephalitis or Encephalopathy: children younger than 24 months with encephalopathy have an explicit or marked loss of consciousness for at least 24 hours which is not caused by intoxication and not explicable as post-ictal state. In children older than 24 months at least 2 of the 3 following criteria must be fulfilled:
  - distinct change in mental status as disorientation, delirium or psychosis not caused by drugs;
  - marked decrease in consciousness not caused by seizures or medication;
  - seizures with (long lasting) loss of consciousness;

  Also signs of increased intra-cranial pressure may be present. In encephalitis, apart from the symptoms of encephalopathy there are additional signs of inflammation as fever and elevated cell counts in the cerebrospinal fluid.
- Anaphylactic Shock: Circulatory disturbance with hypotension and life threatening hypoperfusion of vital organs. This reaction should be in close temporal relation with intake of an allergen and with type I allergic mechanism involved. There may be

accompanying laryngeal oedema or bronchospasm. Urticaria or wheezing alone is not included.

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

Box 7. Main event categories with subdivision according to severity

local reaction	minor	mild or moderate injection site inflammation or other local symptoms
	major	severe or prolonged local symptoms or abscess
general illness	minor	mild or moderate general illness not included in the other specific categories
	major	severe general illness, not included in the listed specific categories
persistent screaming		inconsolable crying for 3 or more hours on end
general skin symptoms	minor	skin symptoms not attributable to systemic disease or local reaction
	major	severe skin symptoms or skin disease
discoloured legs	major	disease entity with diffuse or patchy discoloration of legs not restricted to injection site and/or leg petechiae
faints	major	collapse with pallor or cyanosis, limpness and loss of consciousness; included are also fainting and breath holding spells.
fits	major	seizures with or without fever, epilepsy or atypical attacks that could have been seizures
encephalitis/encephalopathy	major	stupor, coma or abnormal mental status for more than 24 hours not attributable to drugs, intoxication or post-ictal state, with or without markers for cerebral inflammation (age dependent)
anaphylactic shock	major	life threatening circulatory insufficiency in close connection with intake of allergen, with or without laryngeal oedema or bronchospasm.
death	major	any death following vaccination irrespective of cause

5.6 Recording, Filing and Feedback

Symptoms, (working) diagnosis, event category and assessed causal relation are recorded in the notification file together with all other information about the child, as medical history or discharge letters. Severe and otherwise important events are discussed in the periodic clinical conference among the physicians of RIVM, before final assessment, critically reviewing from different angles in order to reach consensus; of this annotation is included in the file. All notifications are, after completion of assessment and feedback, coded on a structured form for future aggregated analyses and annual reports. This coding is entered in the (electronic) logbook in which all incoming adverse events are entered on the date of notification. A single physician does all the coding in order to achieve maximal consistency. This way there is of every notification a time spaced second appraisal. If there are discrepancies, the assessment is discussed with the original appraiser or a colleague. If there is new follow-up information, the case is reassessed and depending on the information, the original categorisation may be adapted. This applies also for the reassessments done the GR committee: 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. Because of the increasing workload, a

less time consuming but equally effective procedure is sought in dialogue with the GR committee. 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 cases to be re-evaluated by the GR committee or offered for second opinion to this committee. A project has been started for a database application, which technically allows for both feedback and aggregated analysis (see paragraph 5.8).

5.7 Health Council

Since 1984 the Health Council (GR) advises the Minister of Health on the safety of the National Vaccination Programme. A permanent committee has been appointed. Currently this expert group includes specialists on the following (different) fields: paediatrics, child health care, public health, epidemiology, microbiology, neurology, immunology, pharmaco-vigilance, pathology, vaccinology. GR base 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 an advisory member of this GR committee. Annually, GR makes a working visit to RIVM to audit the proper procedures and the completeness of registration and the quality and consistence of assessments (commented upon in the GR annual advise to the Ministry of Health). Summarised reassessments of the GR committee are 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 is 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 the workload of the committee had to be reduced and assessment criteria have been agreed upon, only a selection of listed events are reassessed from 1996 onwards, with review of summarised reports of the other events. For the year under report (2002) this change in procedure did have impact on the number of written reports by RIVM and reassessed cases by GR. The committee will include her reassessments in the annual advice to the Minister of Health. A redefining of the task of this permanent committee is at hand, since the safety surveillance as off 2002 is independent from the manufacturer of vaccines. The (planned) reallocation of the vaccine department of the RIVM together with SVM as separate vaccine manufacturer, cut loose from the RIVM, makes the necessity of secondary independent re-assessment by GR less obvious. The broader scientific discussion of particular possible adverse effects within this GR committee will however add to the value of the safety surveillance. RIVM will look for a structured approach for second opinion of selected case reports.

5.8 Annual Reports and Aggregated Analysis

The coded forms are used as data sheets for the annual reports. For 2002 all reported events have been coded by one of us (PEVdB), after reappraisal of the information. Grouped events were checked for maximum consistency. Samples of final diagnosis, causality and categorisation have been discussed in the training programme of new investigators. The development of a robust database is behind schedule; therefore the data for this report have been entered in a temporary (logbook) database with limited possibilities. Trend analysis as planned and more in-depth evaluation will have to wait until the new system is installed.

5.9 Quality Assurance

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

5.10 Medical Control Agency and Pharmacovigilance

From November 2002 onwards RIVM sends expedited reports on so called serious adverse events to Lareb, thus allowing the Dutch medical control agency (CBG) to fulfil its obligations towards WHO and EMEA. RIVM and Lareb have mutually agreed upon the structure and content of these reports. Lareb sends reports directly received from other reporters on programmatically used vaccines to RIVM. These procedures will be fine-tuned in 2003.

6 Results

6.1 Number of Reports

In 2002 RIVM received 1310 notifications of adverse events, on a total of nearly 2.5 million vaccinations with over 6 million vaccine components (the birth cohort is 202,386 for 2002 and 201,748 for 1999 and 207,097 and 204,039 for 2000 and 2001 respectively according to CBS per 22-03-04 [48,49,52]). Of these notifications 21 were compound with two distinct adverse events after one vaccination date. This annual report thus contains 1332 reported adverse events.

These reports involve 1249 children, compared to 1251 in 2001 and 1088 children in 2000. There were 58 children with multiple reports, of which three concerned three different vaccination dates and four multiple reports were also compound and another child had two compound reports. Multiple and compound reports are listed under the respective event categories. In 1998, 1999, 2000 and 2001 there were 26, 44, 40 and 65 multiple reports and nine, eight, 13 and nine compound reports on a total of 1100, 1197, 1142 and 1331 reported events respectively. As described in paragraph 4.2, notifications concerning more than one vaccination date with only mild or common symptoms were booked as single reports unless reported on different dates (table 1).

Table 1. Type of reports of notified AEFI in 2002

notifications	children	adverse events
single	1174[a]	1174
multiple	54[b]	111
compound	17	34
compound and multiple	4[c]	13
total	1249	1332

[a] 28 children had also reports in previous (19) or following (9) years; these are not included
[b] three children with triple reports
[c] one child had two compound reports

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. In 1998 there was a significant increase in the number of reports judged to be partly due to increased awareness and apprehension, further reduced underreporting but to some true increase in actual adverse reactions as well [35]. In 1999 there was again an increase in number of reports. This was to be expected because the change in schedule from march 1999 onwards resulted in a larger number of vaccinated infants of about one month cohort with for dose 1, 2 and 3 approximately an extra 50,000 DPTP/Hib vaccinations. Any change in the programme may give rise to increased apprehension and awareness, which might in turn lead to an increase in notifications also. There appears to be a gradual increase in the birth cohort also up till 2000 and a small

decrease since then. In 2001 there was another increase in the number of reports judged to be possibly due to intensified follow op of the reports both by reporters and by RIVM. Also some better adherence to the accelerated schedule may have played a role resulting in vaccination at on average a younger age with some more young-age specific events reported. (See reports on 1998, 000001 004, on 1999, 000001 005 on 2000, 000001 006 and on 2001, 000001 007 www.rivm.nl). In the current year the numbers are the same as in 2001 both for reports as for children concerned. Details will be given in the following paragraphs.
As in previous years the notification rate is not even over the months, range 63-147, with again the lowest rate in winter.

Table 2. Number of reported AEFI per year (with 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

[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

The first person to notify RIVM about an adverse event is the reporter. As in previous years the vast majority of reports were made by telephone (table 3). Only 50 notifications came by regular mail, most frequently as regionally used, special report forms and some as (hospital discharge) letter. Also some reports came in by E-mail (11) or fax (4). Over the last eight years the absolute number of written notifications fluctuated between 25 and 51. Reports from Child Health Clinics accounted for 81% the same share as in 2001 (varying between 78 and 84% over the years). The parents of 121 (9.1% compared to 8.5% and 8.6% in 2000 and 2001) children were the primary reporters; mostly they were advised to do so by clinic staff. Over the years there has been a slow but steady increase of parental reports from 3.5% in 1994 to 8.6% in 2001. Absolute numbers of parental reports are increasing from 1994 onwards. The other notification sources were more or less stable. See also paragraph 6.6 for information sources.

Table 3. Source and reporting route of AEFI in 1994-2002

		1994	1995	1996	1997	1998	1999	2000	2001	tel	mail	2002	tel	mail
Clinic staff[a]	Physician	474	548	466	547	678	722	687	794	764	30	791	756	35
	Nurse	78	102	116	142	219	221	199	290	285	5	282	279	3
Paediatrician		60	59	56	39	69	70	80	56	52	4	61	49	12
General Practitioner		25	13	26	20	35	34	28	18	18	-	17	17	-
School Health Service		15	18	17	10	31	27	37	31	30	1	39	37	2
District Consultant		9	18	11	16	15	16	5	11	10	1	8	5	3
Parent		25	34	35	40	52	91	97	115	112	3	121	118	3
Other		5	6	2	7	1	9	7	14[c]	8	6	13[b]	6	7
Unknown		21	2	3	1	-	7	2	2	2	-	-	-	-
Total		712	800	732	822	1100	1197	1142	1331	1281	50	1332	1267	65[c]

[a] including staff of refugee clinics (7)
[b] including reports by Lareb (5), KNCV (3), MSN (3), optician (1)
[c] including emails (11) and fax (4) reports

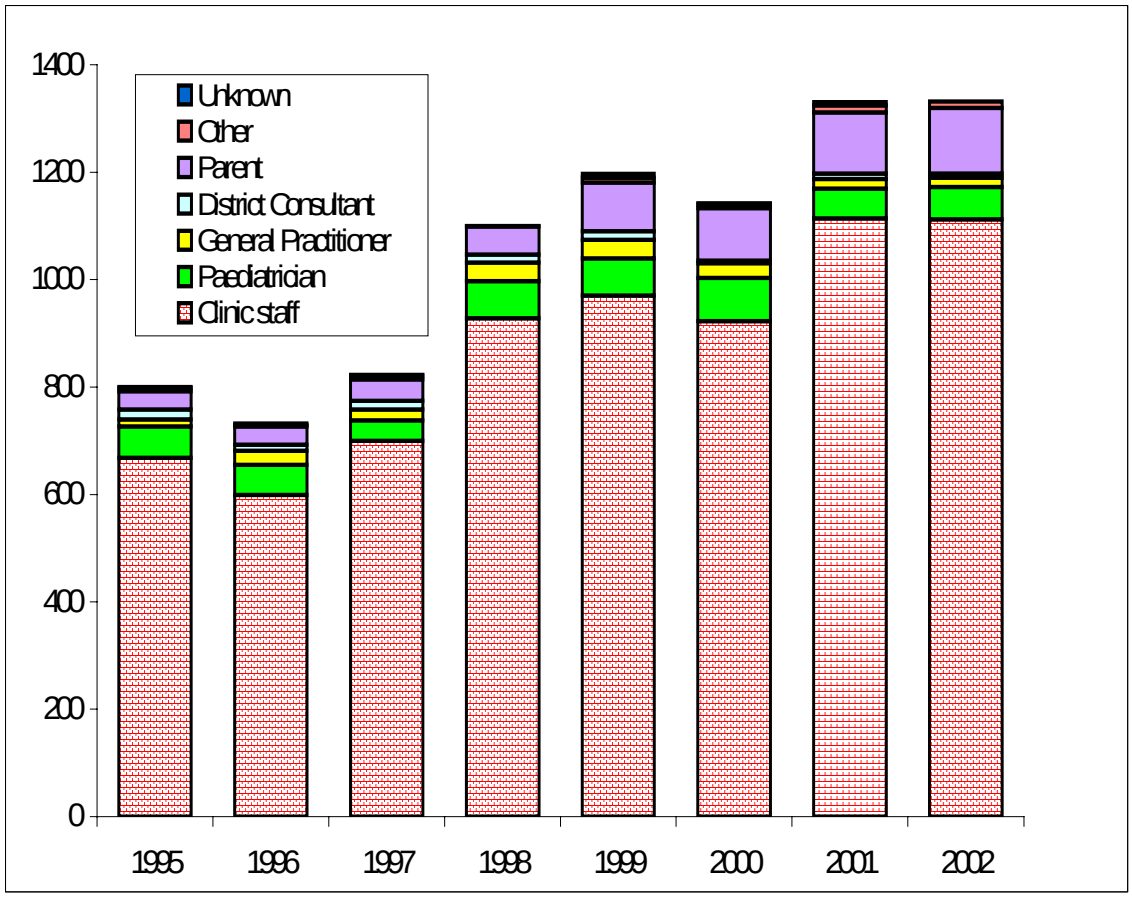


Figure 1. Reporters of adverse events following vaccinations under the RVP

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 4 the rates for 2000, 2001 and 2002 were calculated with vaccination coverage data for the 1999 cohort since data on these birth cohorts have not yet been made available by IGZ [48,49]. Like before we use the coverage data for the first three DPTP doses. For 1999 the rates were adjusted for

the larger number of vaccinated infants because of the accelerated schedule for the first three doses, since March 1999. Since the regular summarised reports of coverage data do not contain information on timing of the vaccination there will remain inevitable inaccuracies in estimated rates per region for this year.

Table 4. Regional distribution of reported AEFI in 1994-2002, per 1000 vaccinated infants[a] with proportionate confidence intervals (major adverse events)

	1994-97 average	1998	95% c.i 1998	1999 [b]	2000 (major)	95% c.i 2000 (major)	2001 (major)	95% c.i 2001 (major)	2002 (major)	95% c.i 2002 (major)
Groningen	3.4	5.3	3.5-7.1	5,1	5.5 (3.7)	3.7-7.4 (2.2-5.2)	4.5 (3.4)	2.8-6.1 (2.0-4.8)	4.0 (2.5)	2.5-5.5 (1.3-3.7)
Friesland	3.9	5.1	3.5-6.7	6,0	5.6 (3.7)	4.0-7.2 (2.4-5.1)	6.6 (3.2)	4.8-8.4 (2.0-4.5)	7.6 (4.9)	5.7-9.5 (3.3-6.4)
Drenthe	2.4	5.8	3.9-7.7	4,4	4.6 (2.5)	2.9-6.3 (1.2-3.7)	3.6 (2.0)	2.1-5.2 (0.9-3.1)	3.0 (2.2)	1.6-4.4 (1.0-3.3)
Overijssel	3.2	4.6	3.5-5.8	4,9	6.5 (3.2)	5.2-7.9 (2.3-4.2)	6.2 (3.4)	4.9-7.5 (2.4-4.3)	6.5 (3.7)	5.2-7.9 (2.7-4.7)
Flevoland	2.5	3.9	2.2-5.6	2,4	4.7 (3.0)	2.8-6.5 (1.5-4.4)	6.9 (4.1)	4.7-9.1 (3.0-5.8)	7.1 (3.5)	4.8-9.3 (2.0-5.1)
Gelderland	3.6	5.2	4.3-6.2	4,4	4.9 (2.9)	4.1-5.8 (2.2-3.6)	5.2 (3.0)	4.3-6.1 (2.3-3.7)	5.9 (3.2)	5.0-6.9 (2.5-4.0)
Utrecht	4.6	6.7	5.4-8.0	6,6	5.2 (2.5)	4.0-6.3 (1.7-3.4)	7.0 (3.6)	5.7-8.4 (2.6-4.5)	7.0 (3.3)	5.7-8.4 (2.4-4.2)
Noord-Holland [c]	3.6	4.7	3.8-5.6	4,0	5.7 (3.6)	4.7-6.7 (3.0-4.3)	5.2 (2.8)	4.3-6.1 (2.1-3.5)	4.2 (2.3)	3.4-5.1 (1.7-3.0)
Amsterdam	6.1	7.2	5.5-9.0	5.6	5.4 (2.6)	3.8-6.9 (1.5-3.6)	8.3 (3.7)	6.4-10.2(2.4-5.0)	6.2 (2.7)	4.5-7.8 (1.6-3.8)
Zuid-Holland [c]	4.7	6.1	5.2-7.0	6,4	5.7 (3.1)	4.8-6.6 (2.5-3.8)	7.6 (4.0)	6.6-8.6 (3.3-4.7)	7.5 (3.7)	6.5-8.4 (3.0-4.4)
Rotterdam	4.3	3.8	2.3-5.3	3.8	5.3 (3.1)	3.6-7.0 (1.8-4.4)	5.5 (3.8)	3.7-7.2 (2.4-5.3)	5.8 (2.5)	4.0-7.6 (1.3-3.7)
Den Haag	5.7	10.8	8.0-13.7	9,4	7.2 (4.4)	4.9-9.4 (2.7-6.2)	9.4 (3.8)	6.8-12.0(3.3-7.1)	6.8 (2.8)	4.6-9.0 (1.4-4.2)
Zeeland	2.2	4.0	2.1-5.9	3,5	5.7 (3.8)	3.4-8.0 (1.9-5.7)	7.8 (5.2)	5.2-10.5(3.6-8.2)	6.9 (5.4)	4.4-9.4 (3.2-7.7)
Noord-Brabant	3.9	5.3	4.5-6.1	6,7	6.6 (3.3)	5.6-7.5 (2.6-4.0)	7.9 (4.5)	6.9-8.9 (3.7-5.2)	8.4 (4.7)	7.3-9.4 (3.9-5.5)
Limburg	4.1	6.2	4.8-7.5	7,0	6.2 (3.9)	4.8-7.5 (2.8-5.0)	8.4 (5.4)	6.8-10.1(4.1-6.7)	9.6 (4.9)	7.9-11.3(3.7-6.2)
Netherlands [e]	4.0	5.6	5.2-5.9	5,6	5.7 (3.2)	5.4-6.1 (3.0-3.5)	6.7 (3.8)	6.4-7.1 (3.5-4.0)	6.7 (3.6)	6.4-7.1 (3.3-3.9)

[a] up till 1999 accurate coverage data are used as published by the Inspectorate of Health Care. Data for 1999 and 2000 have been adjusted accordingly. For 2000, 2001 and 2002 coverage data for 1999 have been used.

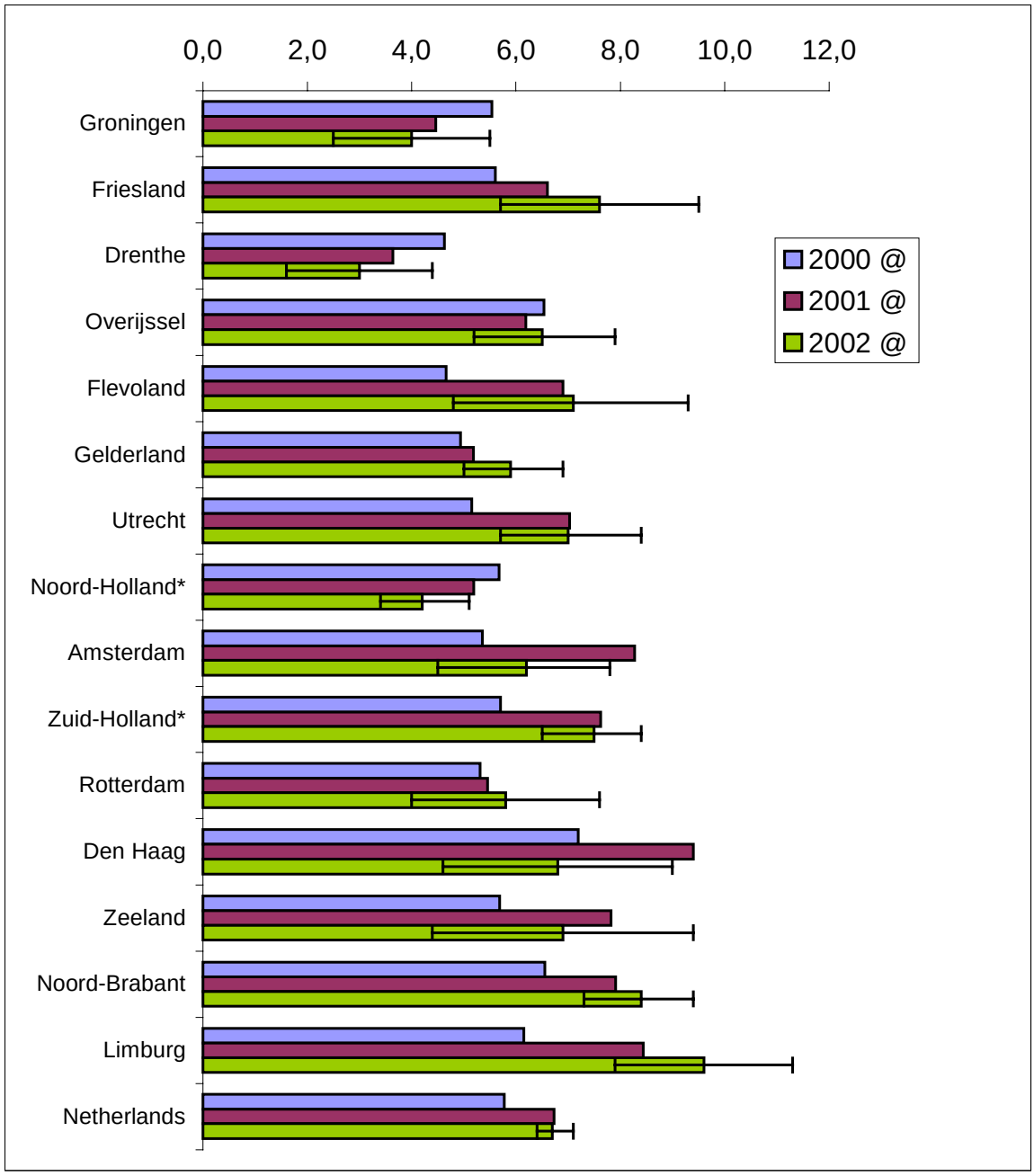
[b] for 1999 figures are adjusted with approximation of higher number of vaccinated infants because of change in schedule.

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

[d] the Netherlands have a birth cohort of approximately 200.000 per year and vaccination coverage of 97% on average for the first three dptp/hib vaccinations.

[e] excluding a few children residing in foreign countries and with unknown habitat

The birth cohort increased from a little below 190,000 in 1996 to 207,097 in 2000 according to the vaccination registers (with according to CBS an small decrease in 2001 and 2002, CBS site per march 2004, 204,039 and 202,386 respectively) [52]. Comparing the different regions does not show relevant differences in rates according to standardisation with coverage data on birth cohort 1999, between 2001 and 2002. Reporting rates for only the so-called major events do not show substantial differences between 2001 and 2002 either. In 2001 there was a substantial increase in both rates compared to 2000. See table 4 and figure 1. We will present and compare differences in numbers of specific events in the respective paragraphs. For 2002 there was a little more dispersion of the reporting rates over the different regions (range 3.0-9.6 in 2002 and 3.6-9.4 in 2001). The 95% confidence intervals for the rates in the different regions contained the country's overall reporting rate in al but three regions however. For the major events only, the differences were smaller (range in reporting rates 2.2-4.9 in 2002 and 2.0-5.4 in 2001).



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

* provinces without big cities Amsterdam, Rotterdam, Den Haag

Figure 2. Number of reported AEFI in 1994 till 2002 per 1000 vaccinated infants (with 95% confidence interval bars, proportional, normal approximation)

6.4 Vaccines

In 2002 most notifications were about recent vaccinations (all except 42). These latter notifications arose from concerns about planned booster vaccination or vaccination of younger siblings; in 36% of these cases parents called. The vaccine involved in these late reports was often MMR (14). Quite often there was (also) concern about the planned menC vaccinations in the catch-up campaign. All reports are included in the tables.
In table 5 scheduled vaccines and actually administered vaccines are listed.
As in prior years, reports on the first DPTP/Hib dose were the most prevalent (503 compared to 515 in 2001), with declining numbers on subsequent vaccinations and older age, respectively 212 (229), 150 (163), 161 (172) for second, third and fourth dose. See for relative frequencies of involved vaccine doses, figure 3. For actually simultaneous DPTP/Hib vaccinations (999) numbers were a little lower than in 2001 (1034), but not significantly different. The number remains significantly higher than the totals of 2000. In 20 reports DPTP was given singly (22, 20 and 16 and 28 in 1998, 1999, 2000 and 2001), without Hib, once with menC however.

Table 5a. Schedule and vaccines of reported AEFI in 2002

vaccine given⇒ / scheduled ⇓	dptp	dptp hib	hib	dptp hib mmr	dptp mmr menC	mmr	mmr menC	dtp	dtp aK	aK	dtp mmr	menC	other	total 2002	2001	2000	1999	1998	1997	1996	1995
dptp1+hib1	5	494[a]	2	-	-	-	-	2[d]	-	-	-	-	-	503	515	418	394	372	323	284	324
dptp2+hib2	2	208[b]	2	-	-	-	-	-	-	-	-	-	-	212	229	191	227	205	142	139	141
dptp3+hib3	6	143[c]	1	-	-	-	-	-	-	-	-	-	-	150	163	133	166	148	103	96	103
dptp4+hib4	4[x]	143[x]	6	4[m]	1[f]	-	-	2[d]	-	1	-	-	-	161	172	166	188	148	95	88	83
dose?	-	5	-	-	-	-	-	-	-	-	-	-	-	5	3	6	8	14	7	4	9
mmr0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	4	-	-	-	-	-
mmr1*	-	-	-	-	-	137[e]	13	-	-	-	-	-	-	150	139	141	139	139	98	80	95
dtp5+aK	3	2	-	-	-	-	-	7	53	1	1	-	-	67	41	33	35	34	22	24	18
dtp6+mmr2	-	-	-	-	-	-	-	3	-	-	32[d]	-	-	35	47	49	33	33	25	13	21
menC	-	-	-	-	-	-	-	-	-	-	-	38[g]	-	38	-	-	-	-	-	-	-
other	-	-	-	-	-	-	-	-	-	-	-	-	11[k]	11	18	1	7	7	7	4	6
total	20	995	11	4	1	137	13	14	51	2	33	38	11	1332	1331	1142	1197	1100	822	732	800

a twice dptp/hib and hepB and once dptphib(aventis)
b once with hepB and once with simultaneous menC
c twice with simultaneous menC
d once with simultaneous hib
e once inadvertently reconstituted in aK and once with simultaneous hib
f fifth dose dptp inadvertently with simultaneous mmr and menC vaccine
g twice inadvertently polysaccharide vaccine menAC
k twice tetanus, twice influenza, twice hepA, twice bcg, once hepA and rabies, twice ppd
m once mmr0, before the age of one year
x once with menC
* mmr and menC from september 2002 onward

For other vaccines or combinations some numbers differ from those of previous years. There were no more reports on MMR1, as yet, of which 13 were with simultaneous MenC, the new addition to the programme from September 2002 onwards (156 versus 157 in 2002 and 2001). MMR1 was given simultaneous with DPTP/Hib somewhat less frequently than in other years. The step up in 1998 in the number of reports on adverse events following MMR1 has been judged decreased underreporting [35].
Numbers of reports concerning the DTP dose at 4-years of age increased further. For the birth cohort (1998), to be vaccinated in 2002, the newly introduced acellular pertussis booster (aK)

was given simultaneously with the DTP booster in 51 reports.
Five children received DPTP5 in stead of DTP and aK, mostly because primary vaccination was not yet completed. 11 children received a single Hib vaccination. Only three reports concerned DPTP/Hib with simultaneous HepB vaccination. Four children received DTP(olio) instead of the scheduled DPTP by parental choice or fear because of prior adverse events (in siblings) twice with simultaneous Hib. The number of reports of events following DTP6/MMR2, always low, was back to the range of 1999 and 2000. The adverse events following MenC are only included in this report if the were part of the vaccination programme (from September 2002 onwards), or given simultaneously with RVP vaccines or by parental choice before the national MenC campaign. Most MenC reports were pre-campaign vaccinations by parental choice. The estimated number of pre-campaign doses was a little over 400,000 doses [53]. The adverse events of the menC campaign will be reported separately (in preparation). 11 Children were reported with adverse events following other non-RVP vaccines. See for further details table 5a and figure 2. The vaccines concerned in the adverse events reported in 2002 are listed below (table 5b).

Table 5b. Number of reported AEFI and vaccines in 2002

vaccine	# of reports in 2002 (2001)	
DPTP	1021 (1072)	Reported adverse events followed DPTP 1021 times in total, mainly with simultaneous Hib vaccinations (999), of which four also received MMR vaccine, three also hepB and four also simultaneous menC. Once DPTP-Hib was from a different manufacturer (Aventis). 19 Reports concerned single DPTP an another two DPTP and simultaneous menC, once also with MMR.
Hib	1031 (1053)	In total 1013 reported adverse events concerned Hib vaccine. In 999 cases Hib was given with simultaneous DPTP, of which four also received MMR vaccine, three also hepB and four also simultaneous menC. Once DPTP-Hib was from a different manufacturer (Aventis). Three reports concerned simultaneous Hib and DTP vaccines, of which one also received MMR. 10 reported events followed single Hib vaccinations and one report Hib with simultaneous MMR vaccine.
MMR	188 (203)	188 reported adverse events followed MMR. 134 of these were single MMR vaccinations, in one case inadvertently reconstituted in aK vaccine. 54 reports concerned MMR with other vaccines simultaneously administered (33 times with DTP in one case also with Hib, 15 times with menC, 4 times with both DPTP and Hib, once with Hib and once with both DPTP and MMR).
MenC	55 (5)	38 children were reported with adverse events after single MenC vaccination, administered by parental choice before the campaign was held, two of these were given the unconjugated meningitisAC vaccine inadvertently. Three reports were about menC with simultaneous DPTP/Hib and one concerned menC with simultaneous DPTP and MMR. Another 13 reports concerned menC together with MMR1 in the regular programme. Thus menC reports total 55 in 2002. The adverse events of the menC campaign will be reported on separately. (in preparation)
DTP	99 (84)	99 reported adverse events followed DTP of which 12 were single administrations. In the other 87 cases DTP was given with other vaccines at the same time (52 with aK, 33 with MMR in one case also with Hib, 2 with Hib)
aK	56 (7)	56 Reported adverse events followed administration of acellular pertussis vaccine, aK. 53 times the vaccine was given simultaneously with DTP. Once aK was inadvertently used as solvent for MMR and once aK was given by mistake in stead of the planned MenC vaccination. Once aK was given as single vaccination at the regular age.
Other	14 (15)	Three reported events followed HepB vaccine with simultaneous DPTP and Hib. Twice influenza vaccine was reported, twice BCG and twice tetanus vaccine all as single vaccines. HepA vaccine was reported three times in one report with simultaneous rabies vaccine. Twice reported events followed PPD skin tests. Only events in Children are included.

Event categories are not equally distributed over the (scheduled) vaccinations (table 6). 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, than at younger ages. No children with anaphylactic shock were reported and no cases of (possible) encephalopathy/encephalitis. Eight children who died were reported. All events are listed irrespective of assumed causal relation. Consult for details the paragraphs on causality and the specific events. Compared to 2001 the total number has stabilised. Within and between the different event categories there are some changes. These will be commented upon in the specific event paragraphs.

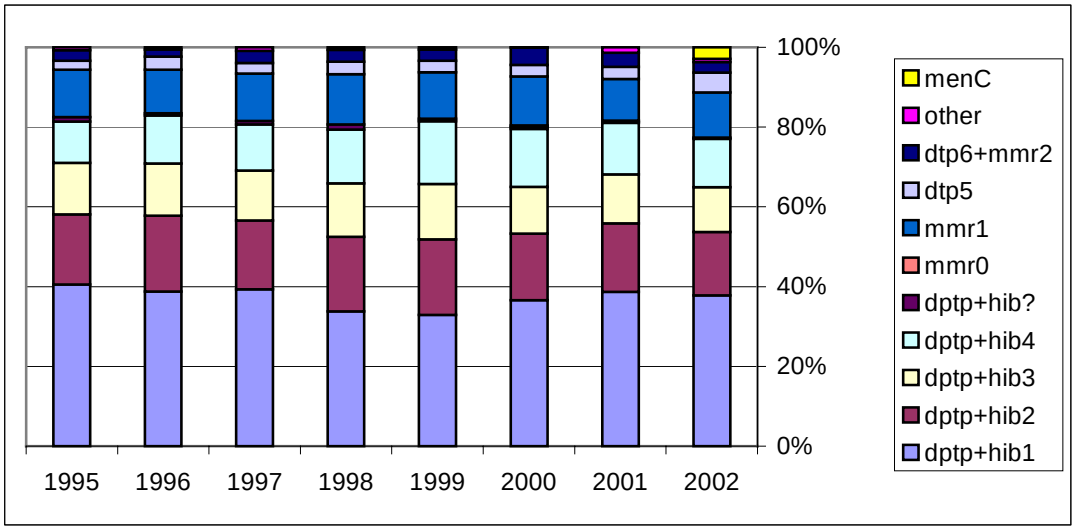


Figure 3. Relative frequencies of vaccine doses in reported AEFI in 1994-2002

Table 6. Event category and (scheduled) vaccine dose of reported AEFI in 2002

event ⇓ vaccine⇒*	dptp/ hib1	dptp/ hib2	dptp/ hib3	dptp/ hib4	dptp/ hib?	mmr 0 or 1	dtp 5	dtp6/ mmr2	menC	other	total 2002	2001	2000	1999	1998	1997	1996	1995
local reaction	18	17	15	27	2	4	15	13	4	5	120	90	75	89	69	49	46	39
general illness minor	141	72	41	61	3	51	20	8	17	3	417	447	366	373	405	254	244	280
major	14	11	17	27	-	30	6	3	3	1	112	74	106	111	85	57	51	55
persistent screaming	33	5	6	1	-	1	-	-	-	-	46	49	39	34	29	26	16	22
skin symptoms	16	14	13	12	-	23	9	6	9	2	104	73	75	85	75	74	58	61
discoloured legs	63	38	23	6	-	1	4	-	2	-	137	175	126	130	125	95	99	93
faints	201	51	21	4	-	-	13	4	3	-	297	293	239	244	174	155	134	147
fits	16	4	10	23	-	37	-	1	-	-	91	121	112	123	133	108	73	97
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	-	-	-	-	-	-	-	-	2	1	1	-	1	2	1
death	1	-	4	-	-	3	-	-	-	-	8	7	3	7	5	3	9	5
total	503	212	150	161	5	150	67	35	38	11	1332	1331	1142	1197	1100	822	732	800

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

The number of reported collapse was comparable to 2001, as were the numbers of persistent screaming and of general illness. The numbers in the category of skin manifestations increased and the number of reported discoloured legs went down, but the number of reported

local reactions increased. Whether this is because of some arbitrary criteria or borderline cases will be discussed in the respective event categories. There was also a decrease in the number of reported fits both in the subcategory of convulsions as in the atypical attacks.
The share of the so called major events in total (714 of 1332, 54%) was a little lower than in 2001 (747 of 1331 events, 56% with 95% confidence interval 53%-59%) but within margins of random fluctuation. See also under paragraph 6.8 on causality.
The relative frequency of the different event categories is more or less the same over the years (figure 4). General illness is the largest category over the years, with a relative frequency of around 40%.
The age distribution is again given in figure 5, comparing 1998 under the old schedule and 2000 and 2001, reflecting the new schedule in the age of the reported children. The current database of the PEA does not allow a precise distribution curve of age at vaccination for the different vaccines for the denominator, only month of vaccination is registered.

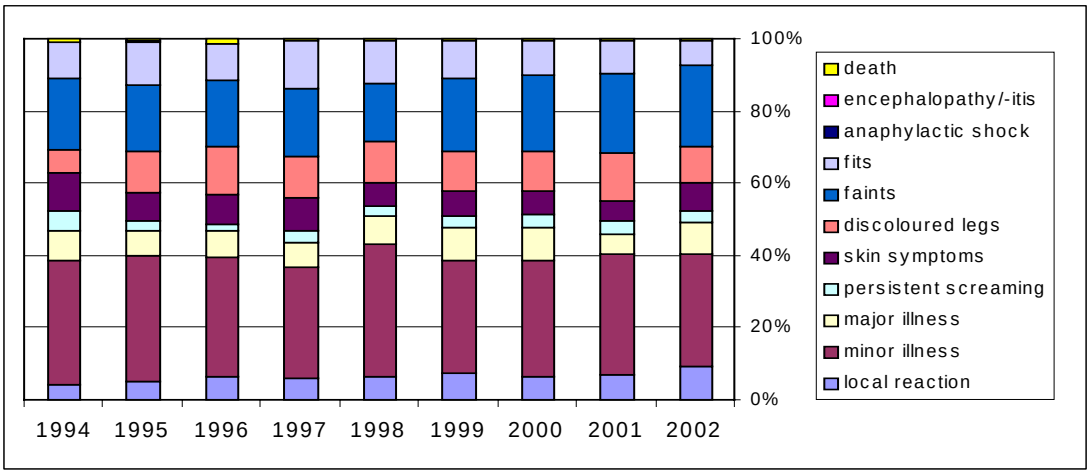


Figure 4. Relative frequencies of events in reported AEFI 1994-2002

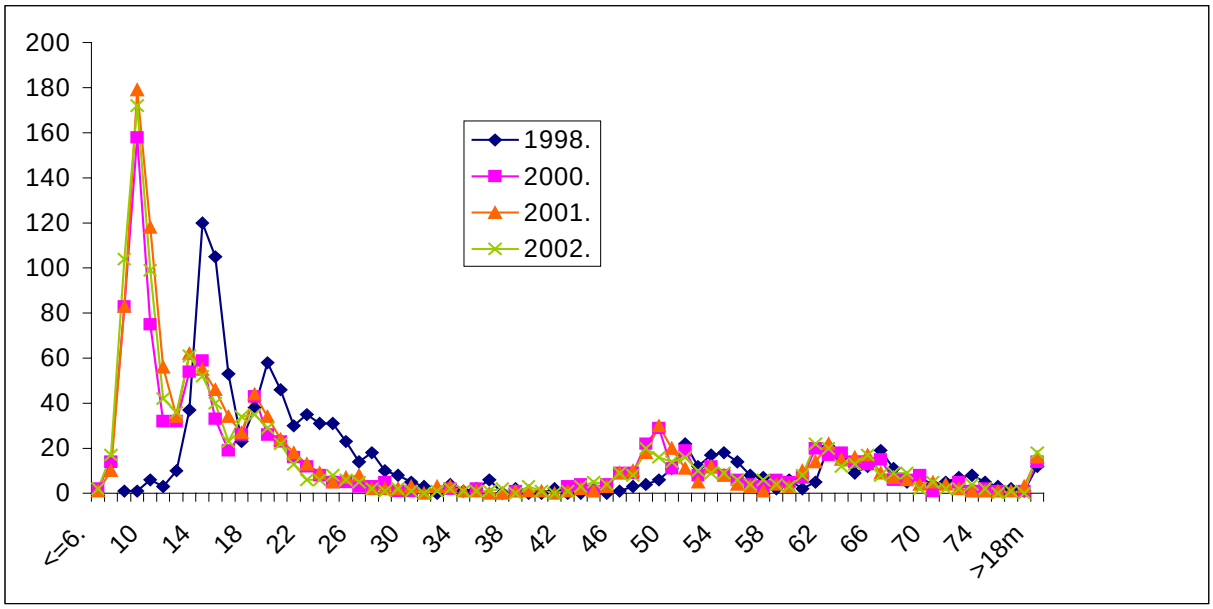


Figure 5. Age distribution of reported AEFI in 1998, 2000, 2001 and 2002

6.5 Feedback to Reporters

Feedback of diagnosis and causality assessment with advice about further vaccinations is a major characteristic of the surveillance system. In about one third of the reports this is (preliminarily) achieved in the notifying phone call. And in about another 10-15 percent final assessment did not change the preliminary evaluation substantially. In over half of the reports however cases could only be assessed after further verification and additional information. In about one fifth the additional information supported the initial information fully. In over one third of notifications the original information lacked essential data. In about one third of the reports the notified diagnosis and/or involved vaccines or time intervals needed adjustment. The feedback, for these reports also, is increasingly done by telephone due to a change in procedures (in 1996) and lack of a robust database system and manpower. The intent is to supply a comprehensive written feedback with assessment routinely. In 2002 6% of reports got a full written assessment, a little lower than in the three previous years (9%).

Table 7. Feedback method and events of reported AEFI in 1998-2002

event ⇓ feedback method⇒	written	tel.	1998 total	written	tel.	1999 total	written	tel.	2000 total	written	tel.	2001 total	written	tel.	2002 total
local reaction	-	69	69	-	89	89	3	72	75	1	89	90	1	119	120
general illness minor	4	401	405	5	368	373	8	358	366	21	426	447	12	405	417
major	14	71	85	21	90	111	18	88	106	14	60	74	20	92	112
persistent screaming	-	29	29	-	34	34	-	39	39	2	47	49	1	45	46
skin symptoms	1	74	75	2	83	85	-	75	75	0	73	73	-	104	104
discoloured legs	1	124	125	9	121	130	5	121	126	14	161	175	4	133	137
faints	9	165	174	18	226	244	17	222	239	34	259	293	20	277	297
fits	14	119	133	11	112	123	15	97	112	22	99	121	16	75	91
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	1	-	1	1	-	1	2	-	2	-	-	-
death	5	-	5	7	-	7	3	-	3	7	-	7	8	-	8
total	48	1052	1100	74	1125	1197	70	1072	1142	116	1215	1331	82	1250	1332

6.6 Source of Information and Medical Intervention

In 2002 in 28% of the notifications the reporter was the sole informer and in 72% information was received from others also, both spontaneously and requested, a little lower than in 2001. (in 2001, 22% and 78%). In 92% of the reports the clinics (child health care, school health and refugee clinics) supplied information. Parents were in 76% (1005) of cases contacted (including the reports in which the parents were the sole reporter), sometimes during the notifying telephone call at the Child Health Clinic. This percentage is a little lower than in 2001 (80%) but higher than in 2000, 1999 and 1998 (66%, 63% and 62%). Parents were the sole informers in 55 cases (21, 40, 41and 52 in 1998, 1999, 2000 and 2001). Hospital specialists supplied information in 16% of the reports the same as in 2001, a little less than in 2000 (18% in 2000 and 19% and 15% in 1999 and 1998).

The level of medical intervention may also illustrate the impact of adverse events. In 21% (277) of reported events no professional medical help was sought or was not reported or recorded by us and 14% of the parents (189) administered paracetamol suppositories, diazepam by rectiole or some skin ointment for instance (in 2001 20% and 13% and in 2000

22% and 12% respectively). 62% of the parents contacted the clinic or GP, called the ambulance or went to hospital, with 10 % admittance. In 1997, 1998, 1999, 2000 and 2001 these latter percentages were 52%, 60%, 64%, 66% and 63% with 11%, 10 %, 12%, 13% and 11% for admittance respectively. Table 9 shows intervention according to highest level used

Table 8. Information sources and events of reported AEFI 2002

info ⇒																
	clinic*	+	+	+	+	+	+	+	+	-	-	-	-	-	-	1229 (92.3%)
	parent	-	+	+	+	+	-	-	-	+	+	+	-	-	-	1005 (75.5%)
	gen. pract.	-	-	-	+	+	-	+	+	+	-	-	+	-	-	48 (3.6%)
	hospital	-	-	+	-	+	+	-	+	-	+	-	-	+	-	214 (16.1%)
	other	-	-	-	-	-	-	-	-	-	-	-	-	-	+	8 (0.6%)
event ⇓	unknown	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
local reaction		57	42	5	2	-	-	2	-	-	1	7	3	1	-	120
general illness	minor	121	221	24	4	4	5	1	1	4	3	19	2	4	4	417
	major	17	51	20	2	2	4	-	-	-	3	6	-	6	1	112
persistent screaming		12	30	2	-	-	-	-	-	-	-	2	-	-	-	46
skin symptoms		26	51	8	2	-	2	-	1	2	1	7	2	-	2	104
discoloured legs		16	94	16	2	-	1	-	-	-	2	4	-	2	-	137
faints		32	206	43	4	-	2	-	-	-	1	7	1	-	1	297
fits		7	37	32	1	2	7	-	-	-	-	3	-	2	-	91
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-it is		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
death		1	-	1	-	2	2	-	2	-	-	-	-	-	-	8
total		289	732	151	17	10	23	3	4	6	11	55	8	15	8	1332

* child health , school health and refugee clinic

Table 9. Medical intervention and events of reported AEFI in 2002

intervention⇒ / event⇓		?	none[a]	supp[b]	clinic[c]	gp tel[d]	gp visit[e]	ambu lance[f]	out-patient	emerg ency	hospital stay	other[g]	post mortem	total
local reaction		13	22	17	26	8	24	-	7	-	3	-	-	120
general illness	minor	49	62	64	42	24	100	2	27	12	13	22	-	417
	major	5	6	15	3	9	25	-	17	3	26	3	-	112
persistent screaming		3	4	25	1	5	4	-	-	1	1	2	-	46
skin symptoms		10	7	2	22	5	35	-	13	3	1	6	-	104
discoloured legs		18	9	26	20	10	33	-	5	6	9	1	-	137
faints		15	42	37	28	34	73	9	6	14	38	2	-	297
fits		5	7	3	1	4	18	7	6	5	35	-	-	91
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		-	-	-	-	-	-	-	-	-	-	-	-	-
death		-	-	-	-	-	-	-	-	-	5	-	3	8
total 2002		118	159	189	143	99	312	18	81	44	130	36	3	1332

[a] homeopathic or herb remedies, baby massage or lemon socks are included in this group, as are cool sponging
[b] apart from 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

6.7 Sex Distribution

Over the years more boys have been reported than girls have. Gradually this has “normalised”. In 1994 and before reports concerned boys in 60% of cases, with a gradual decrease from 1995 to 1998 with then stabilisation to 54% for 1998, 1999 and 2000. For 2001

reports concerned in 51% of cases boys consistent with the composition of the cohorts. In 2002, 52% of the reported events concerned boys (table 10 and figure 6).

Table 10. Events and sex of reported AEFI in 1998 - 2002

event ⇓		sex⇒	1998 m	1998 f	1998 m%	1998 total	1999 m	1999 f	1999 m%	1999 total	2000 m	2000 f	2000 m%	2000 total	2001 m	2001 f	2001 m%	2001 total	2002 m	2002 f	2002 m%	2002 total
local reaction			33	31	52	69	44	42	51	89	34	39	47	75	41	46	47	90	49	64	43	120
general illness		minor	209	185	53	405	201	159	56	373	205	153	57	366	241	194	55	447	214	193	53	417
		major	49	36	58	85	58	53	52	111	63	42	60	106	44	31	59	74	58	52	52	112
persistent screaming			19	10	66	29	19	14	58	34	21	18	54	39	28	21	57	49	28	18	61	46
skin symptoms			40	29	58	75	50	34	60	85	36	35	51	75	39	34	53	73	53	51	51	104
discoloured legs			69	55	56	125	70	58	55	130	65	60	52	126	73	102	42	175	70	67	51	137
faints	collapse		80	77	51	158	119	102	54	221	124	97	56	221	128	140	48	268	141	128	53	270
	BHS		2	2	50	4	-	5	0	5	3	2	60	5	2	3	40	5	4	4	50	8
	fainting		6	5	55	12	9	8	5	18	4	8	33	13	8	11	42	20	9	9	50	19
fits	convulsions		34	31	52	65	37	38	49	77	27	35	44	63	27	28	49	56	28	17	62	45
	epilepsy		1	2	33	3	1	2	33	3	1	6	14	7	2	8	20	10	4	1	80	5
	atypical attacks		37	28	57	65	23	20	53	43	25	17	60	42	34	20	63	55	20	20	50	41
anaphylactic shock			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis			-	-	-	-	-	1	0	1	1	-	100	1	1	1	50	2	-	-	-	-
death			2	3	40	5	6	1	86	7	2	1	67	3	3	4	43	7	6	2	75	8
total			581	494	54	1100	637	537	54	1197	611	513	54	1142	671	642	51	1331	684	625	52	1332

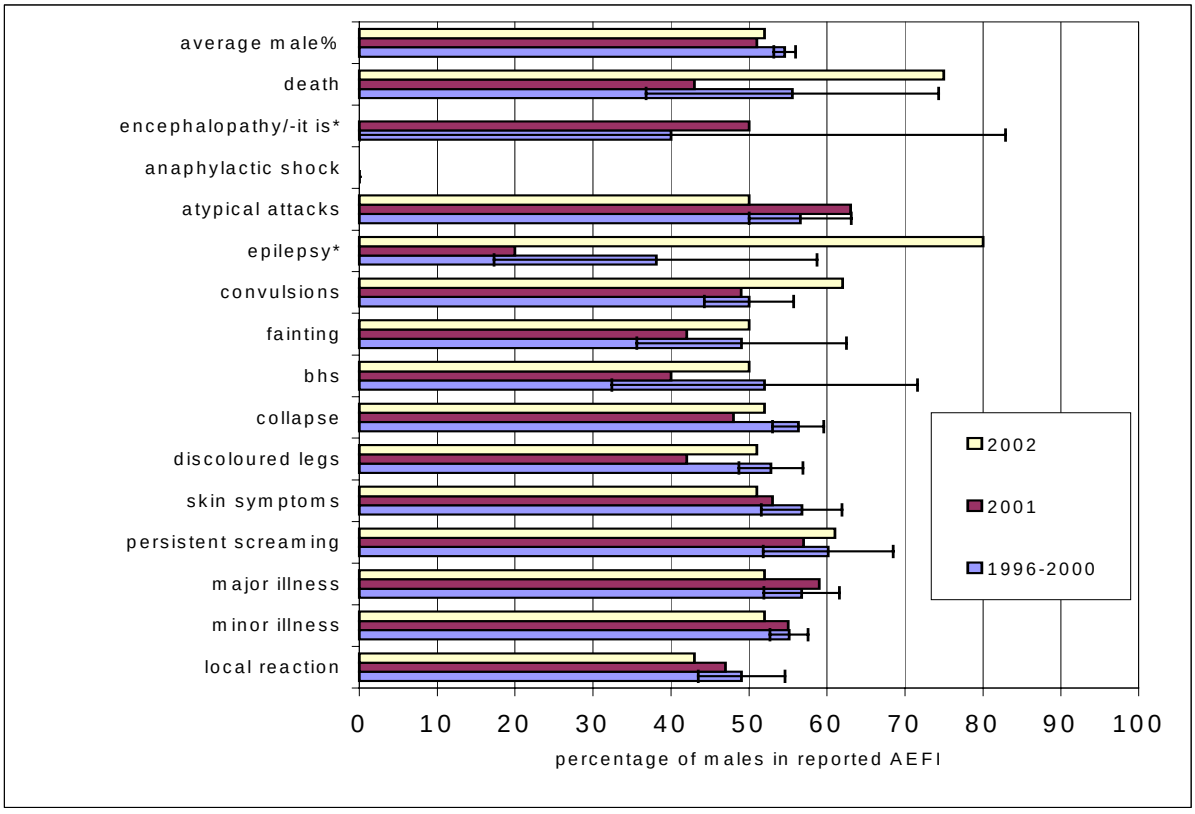


*Figure 6. Events and sex ratio in reported AEFI in 2002 compared to 2001 and to 1996 2000 with confidence intervals (proportional with exact distribution for *)*

Distribution over the different events ranged from 43% boys for local reactions to 62% boys with convulsions, with events with less than 40 reports excluded. See Figure 6.
For 21 children the sex is not known. Under unknown are several cluster reports of minor illness, local reactions and some unsubstantiated rumours. See for specifics on the events and subdivision, the respective categories under paragraph 6.9.

6.8 Causal Relation

Events with (likelihood of) causality assessed as certain, probable or possible are considered adverse reactions. In 2002, 80% of the reports were adverse reactions, a little lower than in 2001 (82%) and a little higher than in 2000 (79%). For 1999, 1998 and 1997 these percentages were 84%, 80% and 80% with exclusion of the non-classifiable events. The other events were considered coincidental events with improbable or absent causal relation with the vaccinations. 12 Notifications were not classifiable (0.9%).
There are great differences in causality between the different event categories, but over the years very consistent (table 11 and figure 7). See for description and more detail the specific paragraphs under 6.9 and discussion in chapter 7.

Table 11. Causality and events of reported AEFI in 2002

event ⇓	causality⇒	certain	probable	possible	improbable	non classifiable	total	(% AR)*
local reaction		70	31	18	-	1	120	(100)
general illness	minor	-	158	130	125	4	417	(70)
	major	-	24	50	37	1	112	(67)
persistent screaming		-	40	5	1	-	46	(98)
skin symptoms		-	3	44	55	2	104	(46)
discoloured legs		-	119	12	6	-	137	(96)
faints	collapse	-	259	5	6	-	270	(98)
	BHS	-	6	2	-	-	8	(100)
	fainting	-	16	1	2	-	19	(90)
fits	convulsions	-	9	29	6	1	45	(86)
	epilepsy	-	-	-	5	-	5	(0)
	atypical attacks	-	12	14	12	3	41	(68)
anaphylactic shock		-	-	-	-	-	-	(-)
encephalopathy/-itis		-	-	-	-	-	-	(-)
death		-	-	-	8	-	8	(0)
Total 2002		70	677	310	263	12	1332	(80)

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

For MMR vaccination 60% of the 188 reported adverse events were considered adverse reactions in 2002. This is higher than in 2001 and 200 (53% and 57% respectively) but lower than in 1999 (69%).
For DTP, DPTP, Hib, aK, menC vaccinations in 80% of the reports possible causal relation was assessed, lower than in 2001 and 2000 (both 87%). For 1997, 1998 and 1999 percentages adverse reactions on the total number of reports were 80%, 88% and 85%, respectively.

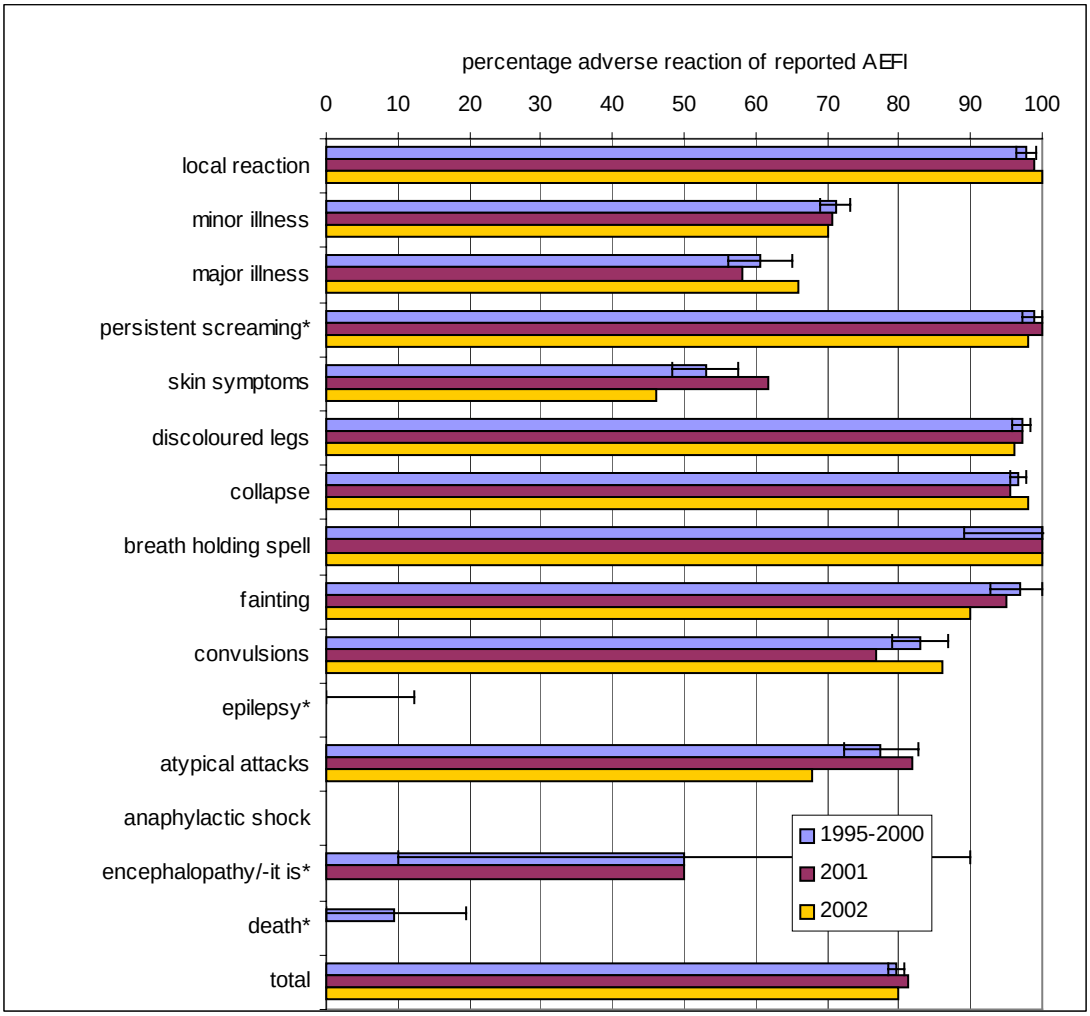


Figure 7. Causality and events of reported AEFI in 2002 compared to 2001 and to 1995-2000 *(with 95% confidence intervals, proportional with exact approximation*)*

6.9 Categories of Adverse Events

Classification into disease groups or event categories is done after full assessment of the reported event. Some disease groups stay “empty” because no events were reported in 2001.

6.9.1 Local reactions

In 2002, 120 predominantly local reactions were reported in approximately equal frequencies after DPTP/Hib or DTP vaccinations (table 12). All but one reported local events were considered reactions, i.e. certainly, probably or possibly causally related with the vaccination. One report could not be classified because of missing information (see table 11).
The exact site of local reactions when more than one vaccine was given simultaneously (94), was not stated in 40 reports of which 28 were unilateral.
The majority of the reported local reactions (98) were mild or moderate. 22 cases were considered so-called major local reactions. Common inflammation was most prevalent (54) of which 8 cases major because of size, intensity or duration. The atypical local symptoms were like some kind of local rash or discoloration (18), possible infection (1),

(de)pigmentation (2), haematoma/fibrosis (2), only swelling, itch or pain (3) or combination of atypical symptoms (4). In 3 of the cases with atypical symptoms the reaction was considered major because of duration and/or intensity of symptoms. In seven children signs of inflammation were mild or absent but there was marked reduction in use of the limp. This is booked separately as “avoidance behaviour”. This was also part of other reactions in 6 cases.

Table 12. Local reactions and vaccines of reported AEFI in 2002 (major events)

vaccine⇒ / event⇓ (major)	dptp/hib1 (major)	dptp/hib2 (major)	dptp/hib3 (major)	dptp/hib4 (major)	dptp/hib? (major)	mmr1 (major)	dtp5 (major)	dtp6/mmr2 (major)	menC (major)	other (major)	2002 (major)	2001	2000	1999	1998
moderate/ pronounced	11 (1)	9	7[b] (1)	6	-	-	9[f](3)	10[h](3)	1	1[k]	54(8)	34(5)	36	39	38
Absces[s]	-	2 (2)	2(2)	1(1)	1(1)	-	-	-	-	2[m](2)	8 (8)	13(13)	9	11	9
pustule	-	-	1(1)	-	-	-	-	-	-	-	1(l)	3(3)	nr	nr	nr
atypical reaction	4	2	1	7	1[c]	3	5[g](1)	3(1)	2(1)	2[n]	30(3)	22(1)	25	32	22
haematoma	1	-	-	1(1)	-	-	-	-	-	-	2(1)	6(1)	nr	nr	nr
nodule	1	4(1)	3	7	-	1[d]	1	-	-	-	17(1)	6(2)	nr	nr	nr
avoidance	1[a]	-	1[a]	5	-	-	-	-	-	-	7	6(0)	5	7	nr
swollen armpit	-	-	-	-	-	-	-	-	1	-	1	nr	nr	nr	nr
total (major)	18(1)	17(3)	15(4)	27(2)	2(1)	4	15(4)	13(4)	4(1)	5(2)	120(22)	90(25)	75(21)	89(22)	69(15)

[a] once dptp only
[b] once dptp only minor reaction and once dptp only with major reaction
[c] cluster report with with local discoloration
[d] once mmr inadvertently reconstituted with aK
[e] all considered major reactions
[f] three times with simultaneous aK, all considered minor reactions and once dptp catch up dose and once dptp and hib catch up dose
[g] four times with simultaneous aK of which once considered major reaction
[h] twice dtp only both minor reactions
[k] tetanus toxoid vaccine
[m] both bcg
[n] ppd

Of the 8 abscesses two were drained surgically and the others drained spontaneously. To our information three times cultures were taken, twice positive for strepA. All abscesses were one-sided, five times DPTP site, once either DPTP or Hib, and twice BCG. No faulty procedures were revealed. One cluster report concerned possibly local pustules, but this could not be substantiated.

6.9.2 Systemic symptoms

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

Minor general illness

In 417 children the complaints were considered minor illness in 2002. After the step up in 1998, considered mainly due to the stronger pertussis component in use, the reporting rates for minor illness have not been significantly different (taking into account the birth cohort with the number of vaccinated children). In 2002, 30% of reports were judged to have improbable causal relation with the vaccination, a little more tan in 2001 (27%) a little less than in 2000 (33%) and in the four previous years 26-28%. See also table 11 and figure 6. Of all reports 76% concerned the scheduled DPTP/Hib vaccinations, most frequently events following the first DPTP/Hib, with the relative share more or less stable over de last five years (table 13). For comparison the numbers of 1994-2001 are included.

Table 13. Minor illness and vaccines of reported AEFI in 1994-2002

scheduled vaccine ⇓	1994	1995	1996	1997	1998	1999	2000	2001	2002	(%AR*)
dptp/hib1	104	102	85	100	117	102	120	158	141[a]	(82)
dptp/hib2	53	54	47	53	81	75	53	65	72	(81)
dptp/hib3	37	46	34	42	60	58	45	56	41	(59)
dptp/hib4	13	27	32	23	54	60	55	63	58[b]	(66)
dptp/hib?	nr	3	1	2	6	5	1	1	3[c]	(33)
dptp/hib+mmr1	nr	2	3	1	-	2	2	3	3[d]	(100)
mmr1	20	31	32	22	62	55	54	63	51[e]	(71)
dtp5+aK	3	6	9	3	11	7	13	16	20[f]	(20)
dtp6/mmr2	5	9	1	7	12	8	23	15	8[g]	(38)
menC	-	-	-	-	-	-	-	-	17[h]	(24)
other	7	-	-	1	2	1	-	7	3[k]	(67)
total	242	280	244	254	405	373	366	447	417	(70)

* percentage AEFI considered adverse reactions

[a] once with simultaneous hepB, once dptp only, once hib only, once dtp only and once dtp and hib
[b] once with menC (pre-campaign), once dptp only, three times hib only and once aK inadvertently in stead of menC
[c] one cluster report
[d] once dptp with mmr and menC, once dptp/hib and mmr0
[e] five times with simultaneous menC under the programme
[f] twice dtp only, once aK only and once dtp with simultaneous mmr
[g] once with hib
[h] all pre-campaign vaccinations, once menAC inadvertently

Only very few times it was possible to make a definite diagnosis; mostly working diagnoses were used. These are listed in table 14.

Fever is the most frequent reported symptom in this category with 70 times the (working) diagnoses. In all but 16 cases the fever was considered possibly causally related with one non-classifiable report. Temperatures were 59 times 38.5-<40.5°C, twice prolonged and another 11 times not measured. Fever was an accompanying symptom in the other (working) diagnoses 195 times (61 times 37.5-<38.5°C, 108 times 38.5-<40.5°C, 26 times not measured).

In 2002 pallor and/or cyanosis was the prevailing symptom, 79 times of which 46 after the first vaccinations, in all but three judged to be causally related. Another 37 times pallor/cyanosis was an accompanying symptom.

Crying was the main feature in 51 cases predominantly following the first two vaccinations, 43 times vehemently and three times prolonged and five times unusually; in three cases the crying had other causes and one was not classifiable. There often was pronounced crying in the other events also (124) or groaning (14).

Irritability once meningismus, was sometimes the (working)diagnosis (5), as were chills (12) and (sleeping) jerks or myoclonics (16), with or without fever, as often as main working diagnosis as in accompanying symptoms.

Apathy or sleepiness was the main feature in 11 cases and gastric-intestinal complaints 26 times.

Respiratory tract symptoms like common cold, tonsillitis, pseudocroup, pneumonia, otitis, asthma, bronchitis etceteras, were frequently diagnosed (24). There were seven children with red urine (myoglobinuria?). Of the 41 children with (possible) rash illness 20 were considered

to be “vaccinitis” following MMR and all of the other 21 were judged to be coincidental events. See for further symptoms and causality table 14.

Table 14. Main (working) diagnosis or symptom in category of minor illness of reported AEFI in 2002 (with number of adverse reactions)

symptom or diagnosis	2000	(AR*)	2001	(AR*)	2002	(AR*)	symptom or diagnosis	2000	(AR*)	2001	(AR*)	2002	(AR*)
fever	71	(56)	87	(70)	70	(54)	pallor and/or cyanosis	52	(52)	77	(75)	79	(76)
low temperature	1	(1)	5	(5)	2	(2)	jaundice	-	(-)	1	(0)	1	(0)
crying	42	(38)	51	(48)	51	(47)	rash (illness)	22	(2)	25	(3)	21	(0)
groaning	1	(1)	1	(1)	1	(1)	vaccinitis	17	(17)	21	(21)	20	(20)
irritability	5	(2)	5	(3)	4	(2)	parotitis	5	(2)	2	(2)	3	(3)
meningismus	-	(-)	3	(1)	1	(0)	swelling face/hands/feet/?	5	(4)	6	(4)	4	(2)
hypertonia	1	(1)	1	(1)	1	(1)	lymphadenopathy	4	(2)	3	(0)	2	(1)
myoclonics	21	(21)	20	(18)	16	(15)	arthralgia/arthritis/coxitis/limping/ falling/disbalance/pain in limbs	3	(1)	6	(3)	6	(2)
chills	10	(10)	14	(12)	12	(11)	allergy/atopy	2	(0)	1	(0)	2	(1)
bulging fontanel	-	(-)	1	(1)	-	(-)	feeding problems	4	(1)	8	(4)	4	(1)
headcircumference ⇑⇑	-	(-)	-	(-)	1	(0)	anaemia	-	(-)	-	(-)	1	(0)
listlessness	4	(2)	3	(1)	4	(2)	vomiting	4	(1)	6	(4)	4	(2)
drowsiness	4	(4)	4	(3)	2	(2)	stomatitis/abscess	1	(0)	1	(0)	3	(0)
prolonged/deep sleep	4	(3)	9	(9)	7	(7)	constipation	-	(-)	-	(-)	2	(0)
behavioural problem/-illness	10	(6)	13	(6)	19	(11)	gastro-enteritis	11	(3)	13	(1)	20	(5)
sleeping problems	5	(0)	2	(1)	2	(2)	myoglobinuria?	1	(1)	2	(2)	7	(7)
apnoea	1	(0)	-	(-)	2	(2)	epidiydimitis/urinary tract infection/haematuria	2	(0)	1	(0)	1	(0)
asthma (attack)/cara	4	(0)	7	(0)	1	(0)	epistaxis	1	(0)	1	(0)	-	(-)
airway infection	10	(0)	9	(0)	12	(0)	headache/migraine	-	(-)	2	(1)	4	(2)
cough	6	(2)	4	(1)	6	(0)	turning eyes	1	(1)	1	(1)	-	(-)
dyspnoea/wheezing	6	(0)	4	(3)	2	(0)	nystagmus/abducens paralysis/squint/anisocoria	1	(0)	2	(0)	3	(1)
pseudocroup	1	(0)	2	(0)	1	(0)	conjunctivitis	-	(-)	-	(-)	1	(0)
tonsillitis/cold	1	(0)	3	(0)	-	(-)	lying still/frozen	8	(8)	9	(9)	6	(6)
otitis	6	(0)	2	(0)	1	(0)	transient episode undefinable	-	(-)	3	(1)	1	(0)
infectious disease	3	(0)	2	(0)	1	(0)	not specified	5	(0)	4	(1)	3	(1)
							total minor events	366	(241)	447	(316)	417	(288)

* adverse reactions

Of the reported AEFI 63 concerned MMR vaccine with in 42 cases a possible causal relation, of which three times attributed to simultaneous DTP, DPTP/Hib or menC. Twice it could be either vaccine. Thus in 62% of the reports of minor general illness following MMR the event was considered adverse reaction to MMR. For the other vaccine combinations this was the case in 68%, with four events not classifiable.

Major general illness

In 2002, 112 reports were classified as major general illness, compared to 74 in 2001, 106 in 2000, 85 in 1998 and 111 in 1999 (table 15). One must bear in mind that the dividing line between minor and major general illness is to some extent arbitrary. To some extent this leads to chance fluctuations within this illness category. If minor and major general illness is taken together then there is no significant difference over the years since the step up in 1998 if number of vaccinated children is taken into account. The distribution in the major illness group is more even over the scheduled vaccines than in the minor illness group. For causality see table 16.

Table 15. Major illness and vaccines of reported AEFI in 2002 (adverse reactions)

diagnosis⇓ vaccine⇒	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	mmr1	dtp5/aK	dtp6/mmr2	menC	other	total (AR*)
high fever	7 (6)	6 (5)	11(11)	24[c](23)	6[e] (3)	3[g](3)	1 (0)	1 (1)	-	59 (52)
chills /myoclonics	1 (1)	1 (1)	-	-	-	-	-	-	-	2 (2)
avoidance behaviour	-	-	-	1 (1)	-	-	-	-	-	1 (1)
gastro-enteritis/dehydration/colitis	1 (0)	1 (0)	2 (2)	-	-	-	-	-	-	4 (2)
myoglobinuria?	1 (1)	-	1 (1)	-	-	-	-	-	-	2 (2)
pneumonia/ bronchiolitis	2[a] (0)	-	-	-	-	-	-	-	-	2 (0)
apnoea	1 (1)	-	-	-	-	-	-	-	-	1 (1)
meningitis/septicaemia	-	-	1[b](0)	-	2 (0)	-	-	1 (0)	-	4 (0)
rash illness	-	-	-	-	-	-	-	1 (0)	-	1 (0)
vaccinitis	-	-	-	-	6 (6)	-	-	-	-	6 (6)
anaphylaxis	-	-	-	-	-	1 (0)	-	-	-	1 (0)
arthritis/osteomyelitis	-	-	-	-	1 (0)	-	-	-	1 (0)	2 (0)
orchitis/epididymitis	-	-	-	-	1 (0)	-	-	-	-	1 (0)
ITP	-	-	2 (0)	-	7[f] (6)	-	1 (0)	-	-	10 (6)
ataxia	-	-	-	-	1 (0)	-	-	-	-	1 (0)
diabetes mellitus	-	-	-	-	1 (0)	-	-	-	-	1 (0)
metabolic disease (derangement)	-	1 (0)	-	-	1 (1)	1 (1)	-	-	-	3 (2)
autoimmune disease (growth failure)	-	-	-	-	-	-	1 (0)	-	-	1 (0)
pervasive/behavioural disorder	-	-	-	1[d] (0)	2 (0)	-	-	-	-	3 (0)
whooping cough	-	3 (0)	-	-	-	-	-	-	-	3 (0)
infection/infectious disease	1 (0)	-	-	-	1 (0)	1 (0)	-	-	-	3 (0)
astrocytoma (pilocytic)	-	-	-	-	1 (0)	-	-	-	-	1 (0)
Total 2002 (adverse reactions)	14 (9)	12 (6)	17(14)	26 (24)	30(16)	6 (4)	3 (0)	3 (1)	1 (0)	112 (74)

* number of AEFI considered adverse reactions

[a] once with hepB
[b] once dptp only
[c] once with mmr and once dptp and menC
[d] once hib only
[e] once with menC and once with hib
[f] twice with menC
[g] once dtp only

Overall, 74 events were considered adverse reactions (65%) a little higher than in 2001 and 2000 (58%). On average since 1995 reported major illness had causality inferred in 60% (range 52%-70%). See figure 6. In the 39 AEFI considered to be chance occurrences the time interval was not plausible and/or other causes were established.
33 Reports concerned MMR with in 15 cases (45%) assessed causality (52% in 2001,40% in 2000 and 43% in 1999) and twice the event was attributed to the other vaccine given simultaneously. For the other vaccines or combinations 59 (68%) reported events were considered to be possible adverse reactions, compared to 60% in 2001, 66% in 2000 and 75% in both 1998 and 1999. See also table 16.
Very high fever (≥40.5°C) was the working diagnosis in 58 cases and in one case fever with delirium. In all but seven cases causality was inferred (including the one case that was not classifiable). In the other events in this category very high fever was present in 18 cases, in five reports because of serious infection and judged to be coincidental. The other 13 cases fever was present in the so-called vaccinitis following MMR1 (6), chills/myoclonics (2), gastro-enteritis (2), and red-urine/myoglobinuria? (2) and extreme avoidance behaviour (1). In other event categories there was very high fever in another 25 cases, mainly in febrile convulsions (21) and atypical attacks (3) since the fever was considered part of the syndrome. These are not listed separately under this major illness category.

Table 16. Major illness and causal relation of reported AEFI in 2002

diagnosis⇓ causality⇒	certain	probable	possible	improbable	unclassifiable	Total	(AR%)
high fever	-	19	33	6	1	59	(90)
chills/myoclonics	-	2	-	-	-	2	(100)
avoidance behaviour	-	-	1	-	-	1	(100)
gastro-enteritis/dehydration/colitis	-	-	2	2	-	4	(50)
myoglobinuria?	-	2	-	-	-	2	(100)
pneumonia/ bronchiolitis	-	-	-	2	-	2	(0)
apnoea	-	-	1	-	-	1	(100)
meningitis/septicaemia	-	-	-	4	-	4	(0)
rash illness	-	-	-	1	-	1	(0)
vaccinitis	-	-	6	-	-	6	(100)
anaphylaxis	-	-	-	1	-	1	(0)
arthritis/osteomyelitis	-	-	-	2	-	2	(0)
orchitis/epididymitis	-	-	-	1	-	1	(0)
ITP	-	-	6	4	-	10	(60)
ataxia	-	-	-	1	-	1	(0)
diabetes mellitus	-	-	-	1	-	1	(0)
metabolic disease (derangement)	-	1	1	2	-	4	(50)
autoimmune disease (growth failure)	-	-	-	1	-	1	(0)
pervasive/behavioural disorder	-	-	-	3	-	3	(0)
whooping cough	-	-	-	3	-	3	(0)
infection/infectious disease	-	-	-	3	-	3	(0)
astrocytoma (pilocytic)	-	-	-	1	-	1	(0)
total 2002	-	24	50	38	1	113	(66)

ITP (Idiopathic/Immunologic Thrombocytopenic Purpura) was reported ten time: four times only through active surveillance by the paediatric surveillance unit (NSCK), twice both through NSCK and passive reporting and four times only through passive reporting. Of the seven cases following MMR1 six were considered possibly causally related. The others were considered chance occurrences. Three children had (suspected) metabolic/hereditary disorder in two of whom derangement was possibly caused by the fever of the vaccine. Two young children had vomiting and/or diarrhoea possibly caused by the high fever. Both were considered adverse reactions. In one child there was possibly apnoea or bradypnoea and causal relation with the vaccination was judged possible although the case missed essential information. All other cases have been assessed very carefully but in none inference of causal relation with the vaccination appeared warranted because of time interval and/or other established causes. The anaphylactic reaction reported was caused by ingestion of a new desert in a severely allergic child, within 15 minutes (8 hours after the vaccination).

6.9.3 Persistent Screaming

In 2002, 46 children with persistent screaming were reported (in 1994-2001 respectively 37, 22, 16, 26, 29, 34, 39 and 49). The reported persistent screaming seems age/dose dependent, as has been noticed in former years (see table 6). Local symptoms were pronounced in only 9 cases, of which six mainly had (presumed) pain at the injection site and twice children avoided moving of the legs more or less completely. Some of the children had both sided local reactions. Additional symptoms were restlessness, feeding difficulty, and pallor. Parents were usually desperate and nine contacted the family physician and two went to the hospital, with one subsequent admission. We did not record the degree of intervention in three cases,

however (table 9). In all but one case the event was considered to be causally related with the vaccinations (table 11). See also under discussion, chapter 7.

6.9.4 General skin manifestations/phenomenon

In 2002 skin symptoms were the main or only feature in 104 reports (74, 75, 85, 75 and 73 in 1997, 1998, 1999, 2000 and 2001). Discoloured legs are not included but are categorised separately. The numbers are considerably higher than in prior years with increase mainly in reported AEFI following MMR1, DTP5/aK and single menC vaccinations. The number of reports considered adverse reactions rose only with two, from 45 to 47. See table 17.

Table 17. Skin symptoms and vaccines of reported AEFI in 2002 (adverse reactions)

vaccine⇒ / symptoms⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	mmr1	dtp5/ak	dtp6/mmr2	menC	other	total (AR*)
angio-oedema/swelling	-	-	-	1	1	2	-	-	-	4
exanthaema	8	7	8[b]	6	14[c]	5[e]	5	4	2[g]	59
harlequin	-	1	-	-	-	-	-	-	-	1
circumscript erythaema arm (vaccine in leg)	-	-	1	1[a]	-	-	-	-	-	2
acrodermatitis	-	-	-	-	1	-	-	-	-	1
ichtyosis	-		-	-	1	-	-	-	-	1
fixed drug reaction	-	1	-	-	-	-	-	-	-	1
loss of hair	-	-	-	-		1	-	-	-	1
urticaria	1	2	-	2	2	1	1	3	-	12
eczema (increase)	4[a]	2	3	1[b]	3	-	-	-	-	13
petechiae	3	1[b]	1	1	1[d]	-	-	-	-	7
diaper rash	-	-	-	-	-	-	-	1	-	1
nail discoloration	-	-	-	-	-	-	-	1	-	1
total 2002	16 (8)	14 (7)	13(6)	12(5)	23(10)	9(4)	6(4)	9(2)	2(1)	104 (47)

* number of AEFI considered being adverse reactions

[a] once dptp only
[b] once hib only
[c] three times with menC
[d] once with menC
[e] once dptp with hib catch up dose
[g] once influenza and once hepA

One child had a severe scaly rash that was later diagnosed as ichthyosis, considered unrelated. All other reports were of minor skin manifestations.
Exanthema, urticaria and (increased) eczema were the most frequent symptoms, amounting to 81%. Four times there was noted vasomotor swelling/angio-oedema without rash and 11 times with exanthema or urticarial rash. Two children had a red swollen arm but were vaccinated in the leg(s). We will address this in the discussion. (See paragraph 7.3.2) There were seven children with petechial rash on upper body and/or face. Children with petechiae on the legs only are categorised under discoloured legs.
23 Cases concerned MMR1 (four times with simultaneous menC vaccination) with 10 times (possible) causal relation, twice attributable to either vaccine. In four out of the six times MMR was combined with DTP there was a possible causal relation in which three times the symptoms could be caused by either vaccine and once was judged to be possibly caused by MMR (interval 7 days). This resulted in possible causal relation with MMR in 48% with

rashes in the second week after the vaccination (without systemic symptoms) or on the day of vaccination when causal relation could not be ruled out.

Table 18. Skin symptoms and causal relation of reported AEFI in 2002

causality⇒ / symptom⇓	certain	probable	possible	improbable	unclassifiable	total	(%AR*)
angio-oedema/swelling	-	-	3	1	-	4	(25)
exanthaema	-	3	25	31	-	59	(90)
harlequin	-	-	1	-	-	1	(100)
circumscript erythaema arm (vaccine in leg)	-	-	-	2	-	2	(0)
acrodermatitis	-	-	1	-	-	1	(100)
ichtyosis	-	-	-	1	-	1	(0)
fixed drug reaction	-	-	1	-	-	1	(100)
loss of hair	-	-	-	1	-	1	(0)
urticaria	-	-	5	7	-	12	(42)
eczema (increase)	-	-	4	9	-	13	(44)
petechiae	-	-	4	1	2	7	(80)
diaper rash	-	-	-	1	-	1	(0)
nail discoloration	-	-	-	1	-	1	(0)
total 2002	-	3	44	55	2	104	(46)

* percentage of AEFI considered being adverse reactions

The other events were not considered causally related with the vaccination, because of inconceivable time interval and/or other cause. For the other vaccines or combinations, possible causal relation was assessed in 38 out of 85 events (45%), with in the remaining events other causes assumed and/or non-plausible time interval. See table 18.

6.9.5 Discoloured legs

Starting from 1995, discoloured legs are in a separate category, subdivided in blue, red or purple legs with diffuse or patchy discoloration, with or without petechial rash. Leg petechiae without noted discoloration are also grouped in this category.
In 2002 137 reports were received, a decrease compared to 2001 (175 and 126 reports in 2000; table 19). Of these 26 were blue legs (26 double-sided), 40 red legs (27 double-sided) and 43 purple legs (39 double-sided). Of the17 cases with one-sided discoloration 6 concerned the DPTP leg and 4 the Hib leg but in 7 cases this could not be decided. In total, 38 children had petechiae, including 23 reports without noted prior discoloration of the legs (31 times both sided). Leg petechiea with or without prior discoloration was reported 31, 30, 33, 28, 31 and 38 times in 1996, 1997, 1998, 1999, 2000 and 2001 respectively.
About 18% (25) of the children had also fever, two ≥40.5°C and listed also in the major general illness category. An additional 34 had low-grade fever (≥37.5°C-<38.5). Over 66% of the children exhibited fierce crying of whom two cried over extended time, not exactly defined (none of these has been categorised under persistent screaming). Injection site reactions, if any were not pronounced, but 15 times severe pain (four times extreme) was noted/presumed, several times without any other signs of inflammation. 12 children had also collapse reaction. These compound reports are grouped under collapse also. 13 children were reported with recurrent discoloured legs after a subsequent vaccination.

Table 19. Discoloured legs and vaccines of reported AEFI in 2002

vaccine⇒ symptoms⇓	dptp/ hib1	dptp/ hib2	dtpt/ hib3	dptp/ hib4	mmr 1	dtp5/ ak	men C	petechiae	total 2002	2001	2000	1999	1998	1997
blue legs	16	6	2	2[a]	-	-	-	1	26	31	23	17	25	23
red legs	18	10	8	2	-	2	-	6	40	63	46	55	56	38
purple legs	22[a]	12[b]	7	2	-	-	-	7	43	56	47	30	30	23
petechiae only	6	9	6[b]	-	-	-	2	23	23	22	9	28	14	11
swollenlimb	1	1	-	-	1	2	-	1	5	3	nr	nr	nr	nr
total	63	38	23	6	1	4	2	38	137	175	126	130	125	95

[a] once dptp only
[b] once with menC

Distribution over the different vaccine doses remained the familiar pattern over the years with reports most frequent after the first DPTP/Hib vaccinations (46%) and decreasing in number with dose number and age. Causal relation with the vaccines was inferred in all but six cases. See table 11 and figure 6. Further details of this specific adverse event will be published in a separate RIVM report (descriptive epidemiology and follow up discoloured leg syndrome following vaccinations, in preparation).

6.9.6 Faints

In this event category collapse (hypotonic-hyporesponsive episode, HHE), syncope (fainting) and breath holding spells (BHS) are listed (table 20).

Table 20. Faints and vaccines of reported AEFI in 2002

vaccine⇒ event⇓	dptp/ hib1	dptp/ hib2	dptp/ hib3	dptp/ hib4	dtp5/ aK	dtp6/ mmr2	menC	total 2002	2001	2000	1999	1998	1997	1996	1995
collapse	198[a]	48[b]	20[a]	4	-	-	-	270	268	221	221	158	145	120	137
bhs	3	3[a]	1	-	1	-	-	8	5	5	5	4	4	7	2
fainting	-	-	-	-	12	4	3	19	20	13	18	12	6	7	8
total	201	51	21	4	13	4	3	297	293	239	244	174	155	134	147

[a] once dptp only
[b] once hib only and once dptp only and once dptp/hib and hepB
[c] twice dtp only

In 2002 there were 270 collapse cases reported, near equal to the number of 2001, but compared to 2000 stabilisation of the increase of 21%. Also reported were eight children with BHS and 19 times fainting in older children. The eight children with breath holding spells turned blue, after stopping to breathe in expiration when fiercely crying, with a very short phase of diminished responsiveness and no limpness or pallor.
The distribution of collapse over the different scheduled vaccines is, as we described before, in the majority of cases after the first DPTP/Hib vaccinations (over 65%) and numbers diminishing with dose number and age [32,40,42]. There seems to be some shift to collapses after the first vaccination of 175 to 201 and some decrease after the second and the third dose (51 vs. 61 and 21 to 30 for 2002 and 2001 respectively) with total numbers remaining the same. This will be addressed in the specific collapse follow up of the 2001 signal [39]. See for further information under introduction, Chapter 1, and discussion, Chapter 7. In 2002 there were 12 children with recurrent collapse reported (versus 18 in 2001 and 5 in 2000), some of

them with rather incomplete episodes and once not collapse but BHS. One of the recurrences one was after Hib only. One compound report was collapse after the same vaccination but was considered not related because of the too long time interval. In another six children with single collapse reactions the collapse was assessed as not related because of the too long time interval and/or other causes (compared to 4 in 2000 and 9 in 2001). See also tables 10 and 11 and figures 5 and 6 for sex distribution and causality.

6.9.7 Fits

In this category (febrile) convulsions and epileptic seizures find a place. Also “atypical attacks” in case definite diagnosis could not be made and convulsion could not be fully excluded either, are listed here. (See also paragraph 5.5)

Table 21. Fits and vaccines of reported AEFI in 2002

vaccine⇒ / event ⇓	dptp/ hib1	dptp/ hib2	dptp/ hib3	dptp/ hib4	mmr1	dtp6/ mmr2	total 2002	2001	2000	1999	1998	1997	1996	1995
febrile convulsion simple	-	-	-	9[a]	13	-	22	26	29	42	39	27	24	23
complex	-	-	1	5	14[c]	-	20	21	26	24	17	18	8	18
tonic	-	-	-	-	-	-	-	2	1	1	2	1	3	10
atypical/not specified	-	-	-	1	1	1	3	2	3	4	3	6	3	7
non febrile convulsion	-	-	-	-	-	-	-	5	4	6	4	5	4	6
epilepsy	1	1	3	-	-	-	5	10	7	3	3	5	3	3
atypical attack	15	3	6	8[b]	9[c]		41	55	42	43	65	45	28	30
total	16	4	10	23	37	1	91	121	112	123	133	108	73	97

[a] once dtp only
[b] once with mmr
[c] once with menC
[b] once mmr0

Most reported convulsions were febrile (42 out of 45), occurring predominantly after the fourth DPTP/Hib (15) and MMR1 (28) vaccinations. No non-febrile convulsions were reported. The atypical attacks tended to be most frequent in the first half year of life (table 21). Fits (convulsions or atypical attacks) at the younger ages were less frequently accompanied by fever than at later doses/older ages, more so in case of convulsions than in the atypical attacks. Altogether 24 children had fever of 40.5°C and over, three times in children with atypical attacks and 21 times with convulsions only once not considered causally related. In all but one, this very high fever occurred in the one year-olds (9 times fourth DPTP/Hib and 14 times MMR1). See table 10 for sex distribution and table 9 for degree of intervention.

Of the 42 convulsions definitely with fever, 38 were possibly due to the fever caused by the vaccination and considered adverse reaction. Of the four convulsions with fever not considered to be causally related, there was other cause established and/or an implausible time interval with the vaccination (three following MMR1, one after DPTP/Hib4). Of the three not specified/atypical febrile convulsions two were considered not causally related with the vaccination, one after DTP6/MMR2 and one after DPTP/Hib4 administration. One report was not classifiable because of missing information (MMR1). See also table 11.

Five children with epilepsy were reported, of which four had (possible) West syndrome. Time interval of the first seizures with the vaccination was several days, one week, 3 weeks

and five weeks. One child had suspected viral encephalitis 10 days after the third DPTP/Hib vaccination with epileptic seizures. Nearly one year later his medication was stopped and seizures did not return. All were considered not caused by the vaccination. All first seizures occurred not in a fitting time window after the vaccinations, making direct influence of the vaccination in triggering the seizure improbable.
41 Reports were classified as atypical attacks, with in 26 cases possible causal relation with the vaccination. In this subcategory there were ten children with possible chills and/or myoclonics. Two children had possible breath holding spells, and 12 children were hypertonic and/or limp. None of the children fulfilled the case definitions for collapse or convulsion.
In 2002 MMR was involved in 39 reports, in all but four as single vaccine.
31 Times causality was inferred with MMR and once the event was attributed to the other simultaneous vaccines. Thus there was imputed causal relation of the fits with MMR in 80% (78% in 2001 and 58%, 86%, 69% and 66% in 2000, 1999, 1998 and 1997 respectively) and for the other vaccines in 59% of reported cases (71% in 2001 and 78%, 85%, 87%, and 76% in 2000, 1999, 1998 and 1997 respectively).

6.9.8 Encephalopathy/encephalitis

In 2002 there were no reports of encephalopathy or encephalitis following vaccination.

6.9.9 Anaphylactic shock

There were no reports on anaphylactic shock in 2002. In one child anaphylaxis occurred 5 minutes after a cow milk desert (“danoontje”) 8.5 hours after the vaccination (see subcategory of major illness). This was considered no adverse reaction to the vaccine. 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.

6.9.10 Death

In 2002 eight children who died following vaccination, were reported (see table 22). These concerned two girls and 6 boys. See the case histories below. Three of the reported cases were late reports, with death in 1999, 2000 and 2001. Twice the reason for reporting was advice for vaccinations of a sibling. In both cases the mother kept wondering about the role of the vaccination in the death of the child. In the other late report it was concern in the neighbourhood that prompted the report. In only three of the eight cases autopsy was performed, however not in all instances inclusive of full toxicological, microbiologic or metabolic work-up or with post-mortem examination of the brain. It should be stressed however that without full post mortal investigation a definite diagnosis is often not possible.

<u>Child A</u>
A boy of 15 months old received his MMR1 vaccination, three days after he had recovered from gastro-enteritis. Eight days later he developed fever and had an airway infection for which he was given antibiotics. A day later he had recurrent episodes with pallor, unresponsiveness and limpness accompanied by fast and deep breathing, like panting. Later on the day he was admitted in the hospital. He had very high blood glucose, for which no

ready explanation was found. After five days he returned home fully recovered. This episode is booked under general major illness with possible metabolic derangement because of fever possibly due to MMR. Five weeks later the boy again developed high fever, for which a paracetamol supp was given. He was listless and wanted to go back to sleep. Some time later he was found dead. Resuscitation was unsuccessful. Autopsy did not reveal cause of death. No post-mortem examination of the brain was performed however. Possibly the child had an undetected metabolic disorder, but screening was unremarkable. The death six weeks after the MMR vaccination was considered unrelated to the vaccination.

Child B

At the time of the MMR vaccination this 15 months old girl had a common cold with green discharge from her nose, but was otherwise not ill. Nearly four weeks later she became sick with fever and a rash. Three days later the GP examined her because of persisting fever and recurrent vomiting. She seemed to improve somewhat later that day. The following morning however she started to vomit and turned blue. When the GP arrived she had stopped breathing. CPR was unsuccessful. Autopsy revealed bacterial endocarditis and direct cause of death herniation of the swollen hypoxic brain. This illness and subsequent death was considered unrelated to the vaccination.

Child C

A boy of four months died suddenly four days after his third DPTP/Hib vaccination. He had a history of surgical correction of coarctatio aortae and open ductus botalli. Autopsy did not reveal cause of death and apart from some symmetric sub arachnoid haemorrhage and a retinal fold, there were no abnormalities. The forensic pathologist could not conclude to traumatic death. In the end the paediatrician with the pathologist concluded the case to be late SIDS. Time interval and epidemiological studies make causal relation with the vaccination remote.

Child D

A 2 months old boy got his first DPTP/Hib vaccinations. He was healthy at that time and had fully recovered from a cold a few weeks before. He had low grade fever later that day. Two days later he became increasingly ill with fever red eyes and problems with stool. Later that day he was admitted to the hospital with suspected septicaemia. Instead of improving his condition deteriorated. He developed Kawasaki syndrome for which he was treated with initially immunoglobulines, prednisolon, ascal and digoxine. He was more or less therapy resistant and had on Ultrasound widening of the coronary arteries. Two months later he died suddenly after vehement crying with unsuccessful resuscitation. Autopsy has not been done. The Kawasaki syndrome and the subsequent complications with fatal outcome are considered unrelated to the vaccinations.

Child E

A 4.5-month-old boy had not many complaints after his third DPTP/Hib vaccination. That night he received once a paracetamol suppository for crying. The next few days were uneventful. Three days after the vaccinations he was found in prone position and cyanotic in

the playpen. Reanimation was to no avail. Autopsy was not performed; cultures of blood, urine and skin were negative. Cause of death was clinical SIDS. Despite the absence of autopsy the death was judged to be not related to the vaccination, because of time interval and for SIDS epidemiological investigation has shown SIDS to be unrelated to vaccination.

Child F

A girl of six months old with Zellweger syndrome received the third DPTP/Hib vaccinations. As always she was ill on the day of vaccination and later that day she developed fever, a cough and became increasingly dyspnoeaic. She was admitted to hospital and died the following day. Because of the poor prognosis of the underlying illness a non-resuscitation code had been decided upon some time earlier. Autopsy has not been performed. Death was because of the Zellweger syndrome; the vaccination may have contributed to the fever however.

Child G

A boy of 14 months old got his MMR vaccination. He had a developmental delay, especially in motor skills. A week after the vaccination he developed fever for which paracetamol was given. In a few days he fully recovered and was playing actively again. 11 days after the vaccination he suddenly became convulsive without fever and developed respiratory insufficiency. After admittance his seizures were therapy resistant. He developed liver failure with toxic levels of his anti-epileptic medication. He appeared to suffer from metabolic disease (mitochondrial) which could explain his developmental retardation, epilepsy and the liver failure. Two month after hospital admission he died because of this metabolic disorder. No autopsy was performed. In this case death was considered unrelated to the vaccination; the initial febrile status epilepticus may have been caused by the vaccination.

Child H

A boy of nearly half a year old had a severe congenital cardiac malformation i.e. hypoplastic left ventricle. Shortly after birth he had his first shunt operation and between the first and second vaccinations a further correction; this improved his haemodynamic situation but clinically his situation remained poor. Later on the day of his third DPTP/Hib vaccination he had a planned check up with the cardiologist. He was tired and somewhat tearful/wimpy but otherwise OK. That night he developed subfebrile temperature and became lethargic, somewhat floppy and breathing became increasingly strenuous. After admittance to hospital his respiration and circulation were insufficient. He died because of right ventricular decompensation. Autopsy was not performed. Death was considered to be due to the severe cardiac malformation. The stress of the vaccination, albeit not pronounced, may have contributed.

Table 22. Death and vaccines of reported AEFI in 2002

child	sex	age[a]	vaccines	time interval illness	time interval death	symptoms/diagnosis	causality[b]	autopsy
A	m	15m	mmr1	5w	5w	fever, with prior episode with fever and metabolic derangement	no	yes
B	f	15	mmr1	3-4w	4w	bacterial endocarditis	no	yes
C	m	4m	dptp+hib3	-	4d	sids? subarachnoidal haemorrhage	no	yes
D	m	2m	dptp+hib1	0-3d		Kawasaki sy. and later complications	no	no
E	m	4m	dptp+hib3	-	3d	clinical sids	no	no
F	f	6m	dptp+hib3	before	<1d	Zellweger sy.	no	no
G	m	14m	mmr1	11d	2.5m	liver failure, toxic levels of anticonvulsive medication and mitochondrial metabolic disorder	no	no
H	m	5m	dptp+hib3	0d	0d	severe congenital vitium cordis with after vaccination hospital check-up; later on that day right ventricular insufficiency	no?	no

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

[b] age at vaccination

7 Discussion

The success of the vaccination programme, having brought the target diseases under control, increases the relative importance of side effects [10,11]. This increases the demands on the safety surveillance system like wise. Mere registration and reporting of possible adverse reactions is not enough to sustain confidence in the safety of the programme [54,55,56]. We will discuss the characteristics of the current enhanced passive surveillance system and comment on its strength and weaknesses. We will discuss how the information in the current system may play a role in the management of adverse events and in the risk-benefit communication to professionals and parents.
The Achilles' heel of passive surveillance is underreporting. Especially selective underreporting creates distortion. Therefore the representativeness of data on AEFI presented here, will be discussed.
The year under report was again given special attention, since this is the third year in which the effect of the change in schedule on some specific adverse events could be further studied. The stabilisation in the number of reports after the increase in reports in 2001 will be discussed as will other trends or signals [36, 44]. 2002 is the first full year in which all 4-year-olds had the aK booster with their DTP. In the latter quarter of the year the menC vaccine was included in the programme simultaneously with MMR1 at 14 months of age. Adverse events following aK and menC will be discussed.
Also there has been increased attention by the public and professionals with regard to the safety of vaccines. This might also influence the number and the type of events reported.
We will discuss the safety of the vaccination programme in the light of the here presented results of the current enhanced passive surveillance system (and with regard to the literature) and consider future approaches.

7.1 Safety Surveillance of the RVP

Safety surveillance of the vaccination programme seems to be of increasing importance [10,11,57,58,59]. The Dutch system has several strong points. Denominators are known, because the PEA register all administered vaccines on individual level [43,49]. The RVP is embedded in the regular Child Health Care with its near total coverage, therefore the programme is delivered by a relatively small group of specifically trained professionals. It is good professional standard in the clinics to ask after adverse events at the next clinic visit and before administration of the next dose. The operation of a (24-hr) central telephone information service for professionals at RIVM is a most important and efficient tool in obtaining notifications. It keeps a close watch on risk perception and programme adherence. Reporting in low-level terms with signs and symptoms and not only 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 results in homogeneous event categorisation. Because of the wide reporting criteria the system allows sensitive signal detecting of new adverse events. The system also allows trend analysis, follow up and some other systematic studies [39,60].

Assessing causal relation is essential in monitoring the safety of the vaccination programme [50,58,61,62,63,64,65]. Of course, after vaccination does not mean caused by vaccination.
Comparison of RIVM with GR assessment shows remarkable consistency. Five different categories are used for causal relation for the purpose of international comparison. However, international comparison is hampered by different criteria for surveillance systems, diagnostic procedures, causality assessment and inconsistent case definitions [66]. On top of that, different schedules and/or vaccines are used.
The Brighton Collaboration, in which RIVM also participates, aims to arrive at defined standardised case definitions for specific adverse events following immunisations. Use of these case definitions is proposed for both pre-licensure studies and post registration surveillance [7,65.]
The current passive surveillance system will need to be supplemented by more active monitoring and systematic studies to test generated signals and hypotheses. The current enhanced passive surveillance however, will remain the backbone of safety surveillance. In a current EU study in several European countries, including the Netherlands, possibilities for improved safety surveillance of vaccination is being explored (EUsafevac) [67,68].
The placement of the safety surveillance system at RIVM with its expertise should guarantee high quality assessment of the safety of the RVP.
The current enhanced passive surveillance system performs satisfactorily. The strength of the system outweighs the inherent weaknesses. See for details the sub paragraphs below and paragraph 7.5.

7.1.1 Information Service, Reporting Route and Feedback

We hold that the telephone service is an important tool in the safety surveillance of the RVP, both for capture of important adverse events or potential adverse reactions and with regard to the quality of data. This low threshold reporting channel has great advantage over written report forms not only because of superior possibility of communication, timeliness and supplementation of data. It is also an important tool for adherence to the programme and to promote proper use of contraindications and it offers guidance to the professionals to ensure adequate vaccination in special circumstances or underlying disorders.
It makes very efficient use of resources, which may be less obvious at the level of RIVM than in the broader perspective of management of the vaccination programme as a whole.
Education of potential reporters, while essential, will not yield much gain in efficiency for the type of reports received in a passive surveillance system. One has to bear in mind that adverse events reported in passive surveillance systems are in majority severe, peculiar, unexpected and rare events, and in case of more common events, concern special circumstances or specific underlying problems. One cannot expect that health care professionals know what specific information is needed for every possible specific event, age and vaccine and keep up with all medical literature in this respect. Education which stresses the importance of reporting and explains the type of basic information necessary to keep at hand when reporting, may contribute to further efficiency gains. Reporting by mail is possible of course, but apparently reporters favour reporting by telephone also since only less

than 4% actually report in writing. Feedback to the reporters of the final AEFI assessment is important. It should be noted in the child's chart. We will in time supply standardised written assessment forms to those reporters that want them, and perhaps offer access to report forms on an interactive website if resources allow. This will have to wait till the installation of a robust database however. Follow up of children with reported adverse events is important. This will increase our knowledge about specific adverse events, risk factors and sequelae and will in turn lead to a safer programme. We will explore how this feedback from the clinics or follow up can be done routinely in a systematic and efficient order.
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 [69,70,71,72]. The RVP communication project of RIVM in close collaboration with other parties will develop factsheets and web based material for parents in spring 2004. Later on this will be followed by 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. We are working on a five-year overview in Dutch in with reported AEFI in 1998-2002, which will, if resources permit, become available in the second half of 2004.

7.1.2 Verification and Assessment

In the monitoring of the safety of the vaccination programme, validation and supplementation of information with follow up is considered of utmost importance. A substantial part of supplementation and verification is done in the reporting telephone call. With written notifications this is much more time-consuming and will have to wait until later.
Categorisation is done according to criteria for diagnosis and case definitions and for causality. For the aggregated analysis all cases have been reappraised. Discrepancy is often quite large between reported symptom/diagnosis and final diagnosis. This discrepancy is partly due to different case definitions, but also because of more detailed further (follow up) information and more specific expertise of RIVM. The value of a detailed account by the parents, especially in case of paroxysmal events, can not be overrated. Careful history taking after the first panic has subsided is of great importance [39,64,73]. Especially collapse reactions are often reported as something else, like ALTE or near-SIDS, convulsion, anaphylactic shock, allergic reaction, encephalopathy etceteras. This is not as surprising as it may seem. A GP with an average of 30 new-borns a year may come across collapse reactions after vaccination only once in 30-50 years! And for paediatricians also it is a rather rare entity with other severe events more frequently encountered. One tends to mould symptoms in known diagnostic categories. But on the other hand, reported collapse reaction does not always fulfil the criteria for collapse. Often there is only pallor or only apathy or just drowsiness or excessive sleep/difficulty in awakening and symptoms do not fit the case definition. The same applies, even more so for reported convulsions.
Skin symptoms tend to cause great concern because of feared anaphylactic reactions following a next dose. Like in former years most children with skin symptoms, even if

apparent/occurring in close time relationship with the vaccination, get a subsequent dose without recurrence. Severe anaphylactic reactions have not been known to happen with the vaccines of the RVP. We prefer descriptive low level terms for skin symptoms as well as for other categories, with no reference to possible pathophysiological mechanisms, like allergic reaction, for which there seems no justification most of the time.
The use of strict case definitions assures homogeneous diagnostic groups with possibility of epidemiological studies for risk factors and sequelae. Together with follow up this may lead to founded adjustment of indications, contraindications, vaccines or schedules as well as to proper precautions when administering a next dose. For collapse reactions this kind of follow up study has shown a low rate of recurrence after further pertussis vaccinations [39,64]. See also under specific events paragraph 7.3.

7.1.3 Reporters

The vast majority of notifications come from Child Health Clinic staff. As professional standards require asking after adverse events routinely and nearly all children attend the clinics this gives good coverage of the safety surveillance. It is expected that few severe events be missed. We try to stress that paediatricians and child neurologists should report more often in training courses. Especially (severe) events or diseases after vaccinations which they themselves hold to be (clearly) coincidental but parents may regard as vaccine associated (later on). This to not much avail apparently. We have used the NSCK (the Netherlands Paediatricians Surveillance Unit) to study two specific adverse events (i.e. ITP and ataxia following MMR or any other vaccine).
It is important even if paediatricians are not the initial reporters that hospital information is made readily available when clinic staff report the event. Only then is it possible to counteract public unrest (pro-actively). This should also enhance the ability of the safety surveillance system to detect new and hitherto unknown adverse events. Reporting by paediatricians or GP's may lead to earlier notifications. It does not make contact with the Child Health Clinics unnecessary however, as the latter have valuable information on growth, development and health and of course data on the administered vaccines. Therefore we have asked clinic personnel to notify anyway, regardless of (supposed) reporting by others. This includes cases where they asked parents to report themselves or heard from the parents that they have done so. Distribution over the different reporting sources has remained stable over the years however, except for some absolute and relative increase in reporting by parents. Events that are more easily missed are those following vaccinations without a close follow up clinic visit. This will possibly affect MMR1 vaccinations to some extent and especially the revaccinations at four and nine years of age. Emphasis will be put on this in training and refresher courses. In the information leaflets for the parents it should be stated more explicitly that in case of severe or peculiar unexpected adverse events, parents should not only contact the GP but (later) also the clinic. In the leaflets of the national MenC campaign in 2002 this phrase has been included with instruction to the municipal health organisation to pass on the reports to RIVM. This has resulted in a high reporting rate and a very close watch on the safety of this mass vaccination campaign. The MenC campaign will be reported on separately

(in preparation). Active follow up as started in the end of 2003, part of which received some financial support from the EU (European research programme for improved vaccine safety surveillance-EUsafevac), should throw some light on the extent of underreporting of some specific adverse events following DPTP-Hib. See also subparagraphs 7.1.6. and 7.2.1.
The number of reports primarily by parents has gone up steadily over the years. This is may be a sign of increased assertiveness of parents butin a large proportion of cases parents are advised to report themselves by the clinic staff.

7.1.4 Source of Information

Information about the adverse event was retrieved from others than the initial reporter in 72% (78% in 2001 and 67% in 2000). See also what is said about this under verification and assessment in subparagraph 7.1.2. Parents were often reporters of AEFI (9%) and they were contacted (actively or spontaneously) for further specific information in 76% of cases. Parents do call the telephone service for professionals for information about the (safety of the) programme, increasingly. Anti-vaccine-movements add substantially to public concern about possible adverse events in the Netherlands as in other countries [74]. Contact with parents is often necessary anyway since permission has to be acquired to request medical information from GP or hospital. More often than not the reporters have insufficient information, necessary for categorisation and causality assessment. Often the reporters do not have first hand information. Hospital information was received in 214 cases with a deficit of around 65 in which the specialist saw the child but we did not receive information despite repeated request and permission by the parents. In the end these cases could be assessed reliably however.

7.1.5 Regional Distribution and Reporting Rates

We have standardised the number of reports per region on rate per 1000 vaccinated infants (for the first three doses DPTP/Hib). Since the actual numbers of vaccination coverage and population in the different regions are only available up till 1999 as yet, the rates for 2000, 2001 and 2002 are based on these data. Apart from the slightly smaller birth cohort ($\pm$ 2% less since 2000, according to CBS data [52]) this is held to have little distorting influence. The overall reporting rate has gone up significantly in 2001 with stabilisation in 2002. Regional reporting rates are consistent with those in 2001 apart from a small decrease for two regions. There was a little more dispersion in the overall regional rates than in 2001, but a little less for the major events only. The overall proportion of major events was a little lower than in 2001, but not significantly so. Trends in reporting rates may be influenced also by the introduction of two new vaccines in the programme (aK and menC vaccine), and must therefore be interpreted with extra care. See for more details under paragraph 7.2 and 7.3.

7.1.6 Passive Surveillance versus Active surveillance

Active surveillance may supplement our enhanced passive surveillance system. Periodic study of tolerability of the used vaccines is warranted, not only in case of signals or expected change in this respect. A planned study for the tolerability of DPTP/Hib got thwarted several times because the planned MenB trial was postponed and in between an accelerated schedule for DPTP/Hib vaccines was adopted. This accelerated schedule however in itself deserves

specific study of overall tolerability at a younger age. In 2004 we plan to complete an active study in about a total of 40.000 doses (for the four doses of) DPTP-Hib for rare and more severe events (EUsafevac). This study serves also the EUsafevac project in which the Netherlands was a partner. This EUsafevac project (2001-2003) for improved vaccine safety surveillance explored possibilities, feasibilities and shortcomings of different designs of safety studies as supplementation of the regular passive safety surveillance in the different member countries. This active study will increase our knowledge of several adverse events, e.g. persistent screaming, very high fever and discoloured leg syndrome for which incidence rates are not known precisely. These outcomes will also be of use in risk communication to providers and parents (paragraph 7.4). This study may also assess the performance of our current enhanced passive surveillance system. Passive surveillance however will remain the backbone of post marketing surveillance and the most appropriate tool in signal detecting. For testing hypotheses generated by passive surveillance systems active follow up through monitoring or data linkage designs need to be employed. With relying on only active surveillance the safety-surveillance-system is “unmanned” for testing generated hypotheses since that will not be possible anymore within the same system. Therefore enhanced passive surveillance as well as designs for hypotheses testing are of importance and should be employed in the right order [75].

7.2 Number of Reports

Since the large step up of 1998, the reporting rate has stabilised in 1999 and 2000. In 2001 however, there was another increase (17%) that cannot be explained by the larger birth cohort (plus 2.5%) or a larger number of administered vaccines. In 2002 the numbers have stabilised however with 1332 reports (1331 reports in 2001). The capacity of the telephone service, the main route for reporting, has been very much under stress in 2000 and 2001, due to lack of resources with possibly subsequent inaccessibility. In 2002 the surveillance system and telephone (information) service have been very much overburdened because of the sudden national MenC campaign which called for intensified safety surveillance both passive and active and subsequent/inherent calls for consultation. This meant more than a doubling of the normal yearly workload without compensation in resources. This may have lead to "evaporation" of notifications, as has been known to happen before when the telephone service was flooded with calls in the period of the last polio epidemic when there was additional shortage of personnel because of illness and vacancies. We have received no signals that notifications have gone up in thin air in the year under report however, but some complaints have come in. Reporters know of course that notification can also be done by mail. There is only very small increase in reporting by mail, however. The telephone service is also used for consultation and advice and since quite a high number of reports reach us because of the need for consultation, we have to assure that the telephone service is “open”, in order not to miss a substantial part of notifications. For 2002 we have taken great care to have open lines over extended hours, both for the menC campaign as for the regular vaccination programme. Our number of telephones consultations more than doubled in this period.

There is a small decrease in multiple reports: 58 compared to the 65 in 2001 (versus 40 in 2000 and 44 in 1999). Minor common events that come up during follow up by RIVM are not included as multiple report unless the events are explicitly reported time spaced. Uncommon and major events are always included in the numbers whichever way the events came to the attention of the surveillance system. This policy has not been changed since 1994. See for criteria the materials en methods section, paragraphs 4 and 5.
The increase in the number of compound reports to 21 (compared to the 11 in 2001) is mainly because a rise in the number of children with high fever not being considered as part of the event (six) and two children reported time spaced with different events following the same vaccination. To some extend criteria for the dividing line between minor and major are arbitrary therefor small fluctuations in numbers may be without meaning. Reporting criteria have not changed either over the years, but awareness of professionals and the public has increased lately, partly because of the publicity around new/to be introduced vaccines. Recently the need for vaccinations and their safety has been questioned by certain groups[13,74]. Public awareness of the seriousness of the target diseases has diminished since the illnesses have been effectively prevented for many years now [76]. Consequently more value is attached to (potential) side effects. This influences the readiness to report perceived adverse reactions. Reporting criteria for adverse events following immunisation are flexible and subject to personal interpretation and circumstances. Our system registers any notification, regardless the reporting criteria, time interval or causality.

7.2.1 Underreporting

Reducing underreporting is of special importance in passive surveillance systems, especially of selective underreporting. Since 1994 we have put extra effort into this, as has been discussed in previous annual reports [33,34,35,36,38]. It has been concluded that the rise in number of reports in 1994-1997 resulted mainly from this effort, with a minor influence of the introduction of a new vaccine (Hib) from July 1993 onwards. The increase in number of reports in 1998 was held to be partly due to a further decrease in underreporting, increased apprehension or awareness, but also to an increase of real adverse reactions caused by the use of the higher potency pertussis component in the DPTP vaccine [35]. The reports of 1999 were difficult to interpret since the change in schedule did not apply to the full calendar year but only to the children born in 1999 (and after) which resulted in vaccination of an extra number of children [36]. The number of reports in 2000 were comparable to 1998, but there was some shift in the type of reported events, held to be due to the effect of the new schedule, with earlier start. The increase in number of reported AEFI in 2001 may be partly due to a decrease in underreporting in some regions with a somewhat larger proportion of minor events in the regions with the highest increase in reporting rate, but this certainly cannot explain the total increase in numbers. The number of reported events is not evenly distributed over all event categories and over all vaccine doses and has changed somewhat in 2002 compared to 2001. See subparagraphs below and discussion of the specific adverse events in paragraph 7.3.

7.2.2 Distribution over Vaccines and Dose

The distribution (relative frequency) of all reported AEFI over the different (doses of) vaccines is rather similar to 1994-2001 (table 5a and figure 3). This gives no indication of selective underreporting and points to very stable reporting habits. The increase in number of reports (17% more) as compared to 2000, is on account of the first three doses of DPTP/Hib. Numbers for the other vaccines are stable. This seems to point to some aspect of those specific vaccine doses. The stabilisation at this higher level of these numbers underlines the need for further investigation of the increase in 2001.
The small changes in the distribution over the different vaccine doses in 2002 are attributable to the new vaccines aK with DPT5 and MenC with MMR1 or singly.

7.2.3 Distribution over Events

The distribution of reports across event categories is also rather similar over the years (table 6 and figure 4). Within each event category over the different (doses of) vaccines some increase/decrease may be random fluctuations. See for specifics the subparagraphs under 7.3. There is no indication of systematic underreporting. The reporting rate of collapse reactions and febrile convulsions have been rather stable and close to incidence rates shown by prospective studies [77,78,79]. However, background rates of most events are not known, and there may be (substantial) underreporting for some. The before mentioned large active surveillance study of 40000 doses DPTP-Hib may supply more insight. The reporting rate of ITP following MMR for instance has been lower than some studies suggest [80,81]. We have followed this up in active study design. See under the specific event in paragraph 7.3. Since reporting criteria include severe events regardless of assumed causal relation, perhaps all severe events, occurring in the applicable risk window for the specific event and vaccine, should be reported. The number of reported discoloured legs has been rather stable over the years, with perhaps some step up since the use of higher potency pertussis vaccine and another step up in 2001. However, we have no indication of the completeness of reporting of this specific event. Therefore discoloured legs are included in the active surveillance that has been supported by the EUsafevac project. Persistent screaming, as we have stipulated before, shows underreporting, in view of estimates in prospective studies (that did not apply uniform case definitions). In some cases, during our assessment of the notifications of persistent screaming, verification showed that some reports did not fulfil the current case definition. This case definition is consistent with the one defined by the Brighton Collaboration [67,82]. In 2000 there was a significant increase in reported collapse reactions possibly because of the change in the schedule. For 2001 there was another increase in collapse reactions may be again due to a further decrease in age of vaccination. In 2002 these figures stabilised, underlining the need for investigation of this signal. Some changes in the numbers of local reactions and skin manifestations and in atypical attacks will be discussed under paragraph 7.3. See for further information 7.2.5 and the specific events under 7.3.

7.2.4 Severity, Reporting Interval, Causality and Level of Intervention

We have checked for the different severity markers/parameters, such as major versus minor events and level of intervention. Parents contacted the clinic or phoned the GP for 242 events

a little less than in 2002 (272) but still a lot more than in the previous years (183, 168 and 94 in 2000, 1998 and 1997), and 588 were actually seen by the GP or hospital specialist (569, 525, 472 and 348 in 2001, 2000, 1998 and 1997). The relative frequency of parents seeking medical help was 62% (63%, 62%, 58% and 54% in 2001, 2000, 1998 and 1997, with 1999 excluded because of unknown denominators). This also seems to point to increased concern if not to increased severity.
The reporting intervals, another indicator of severity or anxiety, for different doses and events have been compared. The reporting interval, did not shorten again, but was again 35% within 4 weeks (before the next clinic visit) as in 2001, compared to 37.5% in 2000 and to 33.4% in 1998. The reporting interval of MMR was, with reporting within 4 weeks in 44% of events compared to 47% in 2001 (41% in 2000 and 34% in 1998). This may have been caused by adverse publicity about safety of the MMR vaccine. But could also be a sign that efforts to enhance the surveillance have worked out well. 60% or the 188 reported events after MMR were considered adverse reactions in 2002. Absolute numbers of adverse reactions following MMR fluctuated between 104 and 112 in the last four years.
For the first three doses of DPTP/Hib, the percentage considered to be adverse reactions was comparable to former years with 86% versus 88% in 2001 (84% in 2000). For the fourth dose of DPTP/Hib the percentage of adverse reactions increased to 79% compared to 76% in 2001 and 85% for both 2000 and 1998. The overall percentage of assessed adverse reactions (with causality assessed as certain, probable or possible) is 80%82% a little higher than on average over the last six years but within range (78%-84%).
The share of major events, by our definition, together with minor events with hospital admission was within range of former years with 55% the decrease attributable to the lower number of diagnosed discoloured legs (56%, 54%, 58% and 58% in 1997, 1998, 2000 and 2001).

7.2.5 Accelerated Schedule

The change in schedule since the 1999 birth cohort did not affect the reporting rate in 2000. The distribution over the different vaccine doses and events was rather similar to before. The younger age at vaccination for the first three doses did not result in a major shift in total numbers and reported events. Therefor, reported events appear to be more dose- than age-specific. It is known that vaccination at a younger age results in less pronounced fever and less local reactions than at a later age [83]. Since the event categories of minor and major general illness are very heterogeneous, the numbers presented here do not yield firm conclusions. The increase in numbers in 2001 was, apart from collapse, discoloured legs, and persistent screaming, mainly due to pallor and crying in the minor illness group. This could be the effect of better adherence to the accelerated schedule with on average younger age at vaccination reflecting the less stable vasomotor system. The increase of collapse reactions in 2000 and 1999 already pointed in this direction. The stable numbers for the other vaccines and doses is in line with this for these vaccinations are not affected by the new schedule. Since PEA data on vaccination do not include the exact day of vaccination we have no precise data on the timeliness of the first three doses. This warrants further investigation to

test this hypothesis. (A feasibility pilot performed in December 2003, in collaboration with the data manager of the PEA on a subgroup of registered children in the northern three provinces, supported this hypothesis.) A special nation wide query in the PEA databases may substantiate or refute this supposition of younger age. Active follow up, as started for the EUsafevac project may shed light on the incidence rates of some of these specific events and on the age at vaccination. See under collapse and discoloured legs below.

7.3 Specific Events

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

7.3.1 Collapse reaction

Reports of collapse reactions appear to have truly increased in 2001 with 21% compared to 2000 but have stabilised again in 2002 (270 vs 268 in 2002 and 2001 respectively). Numbers and distribution over the vaccine doses have been rather stable over the past years, with around 100 reports of collapse following the first DPTP/Hib dose (at three months of age) and approximately 25 and 15 reports after the second and third dose up till 1998. Since the change in schedule the total number of reported collapse reactions has nearly doubled (to 266 in 2002) for the first three doses (OR 1.86, c.i. 1.52-2.27). Distribution again in 2002 over the different doses suggests a strong age effect but also a dose effect since the number of collapse after the first vaccination nearly doubled but after the second vaccination is only half of the number at three months of age before the change in schedule. The number of reported collapse reactions at three months of age, assuming the average age to be the same as earlier with the first dose, would have been about 100 instead of the actually reported 50. We have little reason to believe that this is due to reporting bias or (diminished) underreporting. Apparently, to some extent a previously received dose of DPTP/Hib vaccine protects against collapse reaction at three months of age. Cytokines/mediators/interleukins that are part of the primary immune response but are not formed (as much) following subsequent contacts with the antigens may play a role. We will comment on this in our report on collapse reactions (in preparation).

There were also some reported recurrent collapse, less than in 2001, some with (very) incomplete episodes and two of the recurrences were not collapse but BHS. Once recurrence was after Hib only, showing that collapse reactions are not the primacy of whole cell pertussis vaccines. Since the number is still higher than in the years before the change in schedule. This may be an indication that the accelerated schedule raises the risk on recurrence a little. We plan to look into this more systematically if resources permit.

7.3.2 Discoloured legs

Numbers of discoloured legs are lower than in 2001. But still a little higher than in the previous years. The above made remarks on collapse reactions also apply here. Distribution over the different doses remained the more or less the same, with some effect of the younger age, also suggesting a stronger dose than age effect unless the average age for the second and

third dose still lags behind. Lacking incidence rates of discoloured legs from prospective studies, we can only speculate. The reporting rate of the discoloured leg syndrome has been rather constant since we made it a specific category and applied case definitions, until this year, with however some levelling of the numbers for the first three doses since the new schedule applies. The numbers for the fourth dose remain low. This does not suggest selective underreporting. We will try to estimate incidence rates in the active follow up started under the EUsafevac project. Whether there is some overlap with subcategories under local reactions and skin manifestations will be looked into. The newly reported syndrome of swollen limp or extensive limp swelling (ELS, mainly after subsequent doses of aK vaccine in other countries) seems to be reported in the Netherlands also a few times. Because of lack of uniform case definitions these reports may be in all three categories. We will look for consensus in the Brighton collaboration for this event and (re) apply a consistent case definition on the reported events [84,85].
We will report on discoloured legs in a separate publication (in preparation) that will include some follow-up data on subsequent vaccinations
The number of compound reports with both collapse reaction and discoloured legs rose a little to 12 cases (6, 6, 7, 8, 7 and 8 in 1996, 1997, 1998, 1999, 2000 and 2001). Whether the accelerated schedule increases the risk of recurrence of the discoloured legs or not remains to be seen. Recurrence does happen, not necessarily following the next dose, but remains without sequelae. 12 children have been reported with recurrent discoloured legs in 2002. This will be looked into if resources permit.

7.3.3 Apnoea

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

7.3.4 Convulsions and Atypical Attacks

The number of (classic) febrile convulsions following DPTP/Hib and MMR1 vaccinations were rather similar to 2001, 2000, 1999 and 1998. This is not surprising since these events occur most frequently after the fourth dose, and this dose is not affected by the change in schedule. In 2002 only one febrile convulsion after the third dose of DPTP/Hib was reported. This may reflect the younger age of this dose on average, with subsequent lower (background) rate of febrile convulsions. The number of reported atypical attacks was a little lower than in 2000. Since this subcategory is the dustbin for not easily classifiable paroxysmal events fluctuation in the numbers is not surprising. We follow the reports in this subgroup with scrutiny but up till now no specific trends or signals have come up. The

numbers is this subgroup are (very much) dependent to completeness of information. Thus, in different years transfer to and from other event categories varies. If planning and priorities permit, we plan to look into the phenomenon of atypical attack in more detail. The stable and low number of reports of non-febrile convulsions may reflect non-causality in the first place [79]. In matter of fact no report of afebrile convulsion has been received in 2002.

7.3.5 Local Reactions and Abscess

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

7.3.6 Skin Symptoms and Allergy

Up till 2001 the number of reported skin symptoms remained remarkably stable over the years, with a similar distribution over vaccines and type of efflorescence. In 2002 there was an increase however. This may have been influenced by the introduction of two new vaccines, which may cause increased awareness and apprehension about (allergic) reactions. None of the reported cases were considered to be allergic reaction to the vaccines. With the change in schedule, we expect that more often than before signs of eczema in prone children will follow vaccination. This is not because the vaccine causes eczema but because of the natural history of atopic disease and the accelerated schedule since 1999. The numbers do show some increased reporting however reflecting increased apprehension of vaccination causing allergic disease. Several literature reviews have looked into this. There appears to be no scientific support for this hypothesis [72,86,87,88,89].

7.3.7 ITP, Gait disturbance (ataxia)

ITP numbers have remained low throughout the years. In the year under report numbers have increased somewhat most in the spontaneous reports (six) with another four through the more active NSCK study. Eight cases followed MMR with in three simultaneous other vaccines. In six cases causal relation was considered possible. We conclude so far that this is better reporting en not true increase in adverse reactions. The causal relation of ITP following other RVP vaccines remains speculative. An active surveillance study has been started in 2002 through the Netherlands Paediatric Surveillance Unit (NSCK) in order to gain more insight on ITP and its relation to vaccinations [37,81,90,91]. We will report on the active surveillance through NSCK separately.

Biologically, it is also plausible that MMR may cause ataxia, but there are no systematic data [92]. We get very few reports, maybe because of the lack of causal relation with the vaccine. In the year under report several cases of limping, increased falling have been reported. Only one fulfilled criteria for ataxia. This event followed MMR1 but outside the risk window. The first symptoms were 1 day after the MMR vaccination and nearly two weeks after an airway infection. She recovered after one week. Ataxia has also been included in the active surveillance study through NSCK.

7.3.8 Anaphylactic shock

Most feared of all adverse reactions may be anaphylactic shock. We never had a report of anaphylactic shock caused by the current vaccines of RVP. After so many doses, apparently it does not occur with these vaccines. The practice advocated by IGZ of vaccinating all children in Child Health Clinic settings or mass vaccination at school age seems wise and the non-availability of emergency sets seems justified. There was one report considered to be anaphylaxis, but no shock, within 15 minutes of ingestion of a cow milk desert in an extremely allergic child. The episode was 8 hours after the fifth DTP and aK vaccination.

7.3.9 Encephalopathy

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

7.3.10 Pervasive Disorders and Retardation

Press allegations about possible causal relation between MMR vaccination and autism dented the confidence of parents in the vaccination programme [87,93]. Despite the fact that based on scientific evidence renowned (groups of) scientists have refuted these alleged associations, especially in the United Kingdom and Ireland the vaccination coverage dropped considerably [94,95]. We have received some reports on behavioural problems in the autistic spectrum, often quite some years after the MMR vaccination. Some parents have no real suspicion but have been made insecure, others simply clutch the last straw. In none of the reported cases a causal relation was found, and in some the event preceded the vaccination.
It is to be expected that reports of events that have attracted attention in the press will increase. A passive surveillance system, even an enhanced one, is not the proper tool for a refutation of false hypotheses or for substantiating true ones for that matter. Recently a few systematic studies have been published showing no causal relation of disturbances in the autistic spectrum with MMR vaccination or thiomersal containing pertussis vaccine [96,97].

7.3.11 Epilepsy

In 2001 there has been some increase in reports on epilepsy compared to previous years, concerning very small numbers, in 2002 numbers were very low again however. Numbers

may reflect (public) apprehension. Current scientific data do not support any causal relation between epilepsy and vaccinations. In the past years a number of studies have been done on the aetiology of epilepsies [79]. However, it may not be possible to exclude this definitely in an individual case. Vaccines may cause convulsions, mainly indirectly through fever. As for West syndrome, epidemiological evidence refutes a causal relation [54,98]. However, the age at which it occurs coincides with the vaccination schedule.

7.3.12 Death

This year eight children were reported dying some time after vaccinations under the RVP. In view of the average over the years, this is in line with expectations. Systematic studies and evaluation of the Institute of Medicine have shown infant death to be unrelated to childhood vaccinations [99]. In an individual case, this may not be demonstrated easily. Especially in the case of possible SIDS this poses a problem. Diagnosis of SIDS is possible only after extensive post-mortem examination has not revealed a cause of death. Therefore it is of utmost importance to insist on full post-mortem investigations and to report fully on all infant deaths following vaccinations. Even if causation is very remote, it is known that in the direct surroundings of the case there is an adverse effect on compliance to the programme, of public and professionals. The first three reports in the year under report were at first not directly reported to RIVM, one came initially as part of a rumour. Although substantiation is usually possible with the closely knitted network of child health care, 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.
In the year under report, in none of the cases the vaccination was considered to have played a (direct or indirect important) role in the events leading to death. Since no full autopsy was performed, the cause of death could not be determined in several of the cases definitely. In all causal relation was judged to be unlikely, even without a definite cause of death. In one child having been diagnosed as SIDS the intracranial haemorrhage has not been accounted for fully, and in another the diagnosis of (clinical) SIDS was made. In both the time interval was outside the risk window for the vaccines concerned. Two children died on the day of vaccination. Both had a severe underlying disorder that would be fatal in time. Therefore in both cases attribution of the vaccination to the time of death is considered to be remote.

7.4 Management of Adverse Events

The increasing relative importance of potential side effects makes careful surveillance of the safety of the vaccination programme even more important than before. Just signal detection isn’t enough. See also under paragraph 7.1. Evaluation and feedback communication should

complement mere registration. Signals should be followed up with more systematic studies. Information about reported adverse events should have a place within the risk communication to parents. Some side effects are unavoidable, but where possible the aim should be to prevent side effects. Adverse coincidental events are truly chance occurrences however. Sometimes postponement of vaccination might free the vaccine and the vaccination programme from allegations of causing an event or disorder that would inevitably have occurred. But deferral should be avoided as much as possible because it will delay protection of the child.

7.4.1 Prevention and Treatment Adverse Events

Adverse reactions or side effects do occur and parents should know what to expect. They need instruction about what (not) to do to alleviate symptoms. In the communication about the risk of vaccination, attention should be paid to the decrease in (awareness of the risk of) occurring target diseases. It should however also be stressed that not everything occurring after a vaccination is indeed caused by the vaccine. One of the most severe adverse events is undue, even fatal delay in recognising severe coincidental illness, because for too long the vaccine was thought to be the cause of the illness [32,33,34,35,36,38,39]. Some education of the professionals in this respect seems warranted also. The vaccination as cause should be in the differential diagnosis, nothing less but at the same time nothing more.
Proper procedures and techniques are important in minimising adverse reactions and the proper use of paracetamol should be included in the information to parents.

7.4.2 Contraindications

Contraindications for the RVP vaccines have been abandoned more or less completely [39,42,44, 61,62]. Proper application of true contraindications should be adhered to however to prevent undue side effects. But false contraindications should be avoided on the other hand because they lead to missed opportunities to provide protection. In the year under report abandoned contraindications do not seem to have contributed much to the number of reported events. And therefore prevention of side effects will not gain much in using more strict contraindications and only result in a loss of protection.

7.4.3 Risk Communication

In our telephone information service and in our adverse event surveillance system we are (made) increasingly aware of the need of (at least a group of) parents for more balanced and readily accessible information about the pro’s and con’s of the vaccination programme. More and more providers signal the need for more apt and specific information to be communicated (by them) to parents. The providers may the best-informed professionals in vaccination matters but they also need timely information for their own reflections. They do need up to date facts and figures. Providers and parents should be systematically informed about the risk-benefit balance of the programme. The successful control of the target diseases has diminished awareness of the severity of the target diseases and increased the perceived risk of complications and sequelae. Child Health Care personnel should be equipped with more direct and adequate and up to date information and need up to date information on matters of vaccine safety. The present anti-vaccine-movements and the confusion they create make this

argument more compelling. The Minister of Health has recognised the need for this repeatedly and answered as much to questions by members of the parliament repeatedly. Only halfway 2003 the necessary funds have been allocated to RIVM and since than 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 schooling 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 en from mid April 2004 on www.rijksvaccinatieprogramma.nl.

7.4.4 Causality Assessment

Causality assessment is important for surveillance purposes of the vaccines, the vaccination programme and for the individuals concerned [41,42]. Individual continuation of the schedule depends on proper assessment. It is important for the entire population served also, as inquietude and commotion will result in diminished coverage. One should acknowledge genuine adverse reactions and recognise evidently coincidental events both. Careful causality assessment will exonerate the programme from severe but unrelated adverse events. It will also detect new rare adverse reactions and as yet new unrecognised more common side effects. Therefore thorough causality assessment will enhance the safety of the programme.

7.5 Considerations for the Safety Surveillance of the RVP

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

The tolerability of the currently used vaccines might be measured, partly in the phase II and III trials in which the registered vaccines are used in the control groups. But in case of changes in schedule or of included already registered vaccines active tolerability monitoring should be included in comparative design (pro-actively thus) [75]. This can not be left to the (different) involved manufacturers but should be a standard part of programme surveillance. Standardised case definitions and reporting criteria are a must [66].

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

Active surveillance to check on overall tolerability of known but more rare events following the vaccinations has been started under the EU project (EUsafevac, to explore feasibility and constraints); the outcome of this active study with scientific data on incidence rates among others is of direct importance for the safety surveillance of the programme. Gait disturbances (ataxia) and ITP after MMR1 are also studied events in active design through NSCK. These

studies may shed light on ITP and gait disturbances as adverse events. All these data may qualify the relative performance of the current enhanced passive surveillance system.
A well performing, good quality passive safety surveillance system such as exists in the Netherlands should not be taken for granted but requires maintenance and investment. On the other hand shortcomings as overdue privacy concerns and the absence of outcome databases or common personal identifiers, that may be used for data linkage purposes, should be addressed. Without the use of these new epidemiological designs that may expand our knowledge of adverse events may be hampered. An adequate database system is a prerequisite for this as well. The data put into the system must be of good quality nevertheless, therefor this should get a lot of attention. “Rubbish in rubbish out” also applies to safety surveillance.
After successful prevention of the target diseases the relative weight of adverse events increases. Parents and providers expect careful safety monitoring of the vaccinations. Anti-vaccine-movements will be more active in the future. A comprehensive surveillance system will be instrumental in refuting unfounded allegations.
Providers must be supplied with timely and adequately referenced information about any suggested association of severe adverse events and vaccination in the media or medical press. This will enable them to answer questions from the public. Clinic staff stresses that convincing parents of the benefits of the vaccination programme takes more time than before and indicates that resources fail. Often parents already have information from other sources and it is not easy, if at all possible, for them to decide on its quality. The sites of anti-vaccine movements on the Internet are much more readily accessible than the more balanced information about the merits of the programme. There is increasingly need for fact sheets per target disease and per vaccine. The possibility of adverse events in general and how to act as parents in case of should be addressed. Periodic actualisation of the RVP guideline book is also necessary but these updates will lag behind and not meet the need for timely information to inform on or refute false allegations. Lately the Minister of Health has recognised this need in a letter about the RVP to the parliament (2nd of October 2000) and repeatedly in answering questions of members of parliament. The start of the project for improving public information on the vaccination programme in 2003, with the launching of a web site is a first step in meeting some of the above discussed needs. Intensified study of specific adverse events through different designs should also be addressed systematically, with follow up of signals detected. Timely allocation of funds is needed with long term commitment.

8 Conclusions and Recommendations

In 2002 the number of reported events stabilised to the level of 2001, after the rather unexpected rise in 2001. This underlines the need to study the explanatory factors for this increase. The use of the higher potency whole cell pertussis vaccine has caused an increase in reports. The change in schedule in 1999 has not led to an overall increase in reports initially. There was however an increase in reported collapse reactions, which has nevertheless continued in 2001 with an increase in reported discoloured legs, and other symptoms believed to be young-age specific. This has led to an overall increase in the number of reports of 17% and to 21% increase in those specific events. This may be an indication that the earlier start of the vaccination schedule plays a role in these events and might be related to better adherence to the new schedule in 2001. This warrants further investigation, as does the possible rise in number of recurrent collapse reactions. This will have to be subject to further study if resources permit.

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

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

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

The planned database system for adverse event surveillance should allow further detailed aggregated analysis of the reports and also facilitate systematic feed back to the reporters as well as data exchange with other bodies, nationally and internationally. Safety surveillance systems in the future should be prepared to study generated signals of specific rare or long-term adverse effects on short notice. Especially now that introduction in the RVP of more (novel) vaccines is expected in the forthcoming years (foreseeable) safety concerns should be included in the discussion about introducing the vaccines in the programme. Stratified introduction could be helpful, preferably a little more systematic and time spaced than in the MenC campaign [100,101].

Only then will it be possible to study new suspected adverse reactions properly and to adequately counteract allegations of anti-vaccine movements. 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 planned:

- implementation of a robust database system
- accelerated annual report on 2003 and on the menC-campaign
- maintenance and evaluation of the current passive surveillance system
- report on descriptive epidemiology of discoloured legs and follow up also with regard to the accelerated schedule and rate of recurrence
- belated report on descriptive epidemiology of collapse reactions and follow up, also including the effect of the accelerated schedule
- further exploration of possibilities of data linkage or sentinel studies, to test generated hypotheses.
- continuation of active study of incidence rates of some acknowledged but not so common adverse events following DPTP-Hib vaccinations, also in relation to the accelerated schedule with start of the programme at a younger age.
- active follow up of changes in the programme.

We plan to keep up a thorough high quality safety-surveillance-system and to stimulate reporting in the coming year. Thus, one can show that the vaccination programme is safe. The total of 1332 reports must be seen in relation to a total of 2.5 million vaccines administered with over 6 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 of 2001

STAATSTOEZICHT OP DE VOLKSGEZONDHEID

Inspectie voor de Gezondheidszorg

RIJKSVACCINATIEPROGRAMMA 2002

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

2002	2001	1996	1993
DKTP + Hib	DKTP + Hib + BMR	DTP + aK	DTP + BMR

1 ALGEMEEN

1.1 Organisatie
De uitvoering van het Rijksvaccinatieprogramma wordt verzorgd door Thuiszorgorganisaties en GGD's, 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 de SVM (Stichting tot bevordering van de Volksgezondheid en Milieuhygiëne) afgeleverd aan de Entadministraties. De distributie en het gebruik van de vaccins geschieden onder administratief toezicht van de Entadministraties.
De verstrekking van de vaccins vindt uitsluitend plaats na aanvraag van de gebruiker(s) bij de Entadministraties en onder voorwaarde dat de vaccins worden aangewend voor de uitvoering van het Rijksvaccinatieprogramma of in bijzondere omstandigheden volgens richtlijnen te geven door of namens de Minister van Volksgezondheid, Welzijn en Sport.

1.3 Registratie en verantwoording
De vaccinaties worden bij de Entadministraties geregistreerd en verantwoord aan de hand van de teruggontvangen oproepkaarten.

1.4 Financiering
De kosten van de uitvoering van het Rijksvaccinatieprogramma komen ten laste van de in de AWBZ geregelde verzekering.
Per verrichte vaccinatie wordt een bedrag uitbetaald aan de Entadministraties. De Entadministraties zullen volgens landelijke richtlijnen zorgdragen voor doorbetaling van de ter beschikking gestelde gelden aan de uitvoerende organisaties. Voor vaccinaties in het kader van het Rijksvaccinatieprogramma door de Thuiszorg of GGD behoeven de ouders geen bijdrage te betalen. Indien ouders nadrukkelijk kiezen voor een ander dan het in het schema aangegeven vaccin of voor een afwijkend tijdstip van vaccineren komen zij niet voor de gratis verstrekking in aanmerking, tenzij voor de afwijking een medische indicatie bestaat.

1.5 Kinderen tot 13 jaar die, anders dan door de nadrukkelijke keuze van de ouders, niet of niet volledig zijn gevaccineerd volgens het voor die jaarklasse geldende vaccinatieschema, kunnen de nog **noodzakelijke** vaccinaties kosteloos ontvangen in het kader van het Rijksvaccinatieprogramma.
Dit geldt uitsluitend voor de DKTP-, DTP- en BMR-vaccinaties.

5 BIJWERKINGEN

Na vaccinaties kunnen in zeldzame gevallen (ernstige) bijwerkingen optreden.
Elke bijwerking kan de vaccinatiegraad negatief be nvloeden. Elke ernstige, onverwachte en/of onrust veroorzakende (mogelijke) bijwerking dient gemeld te worden aan het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) te Bilthoven, onder vermelding van het partijnummer van het betreffende vaccin (tel. (030) 274 24 24; fax (030) 274 44 30; Email: ribris@rivm.nl).

6 VACCINATIESCHEMA PER KIND

Leeftijd	Vaccinaties
2 maanden	DKTP-1 + Hib-1
3 maanden	DKTP-2 + Hib-2
4 maanden	DKTP-3 + Hib-3
11-12 maanden	DKTP-4 + Hib-4
14 maanden	BMR-1
4 jaar	DTP-5 + aK
9 jaar	DTP-6 + BMR-2

7 ENTADMINISTRATIES

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

	Adres	Telefoon/Fax	E-mailadres
GRONINGEN-FRIESLAND-DRENTHE	Gorechtkade 8, 9713 CA Groningen	Tel. 050-3686350 Fax. 050-3122733	[illegible]
OVERIJSSEL-FLEVOLAND	v. Reeuwijkstraat 50, 7731 EH Ommen	Tel. 0529-455717 Fax. 0529-455805	[illegible]
GELDERLAND	Korte Coehoornstraat 2, 6811 LB Arnhem	Tel. 026-4425242 Fax. 026-4434099	[illegible]
UTRECHT—NOORD-HOLLAND	Computerweg 6, 3542 DR Utrecht	Tel. 0346-550040 Fax. 0346-573796	[illegible]
AMSTERDAM	Nw. Achtergracht 100, 1018 WT Amsterdam	Tel. 020-5555480 Fax. 020-5555071	[illegible]
ZUID-HOLLAND	Europaweg 141, 2711 EP Zoetermeer	Tel. 079-3418238 Fax. 079-3315047	[illegible]
ROTTERDAM	Schiedamsedijk 95, 3011 EN Rotterdam	Tel. 010-4339517 Fax. 010-4339652	[illegible]
ZEELAND	Noordsingelstraat 23, 4461 GR Goes	Tel. 0113-224000 Fax. 0113-224055	[illegible]
NOORD-BRABANT	Bosscheweg 57, 5056 KA Berkel-Enschot	Tel. 013-5400088 Fax. 013-5400086	[illegible]
LIMBURG	Dalderhaag 13, 6136 KM Sittard	Tel. 046-4520910 Fax. 046-4584479	[illegible]

De Inspecteur-Generaal voor de Gezondheidszorg

Prof. dr. J.H. Kingma

Den Haag, december 2001

Voor de Hib-vaccinaties geldt dat in het kader van het Rijksvaccinatieprogramma alleen kinderen die geboren zijn vanaf 1 april 1993 voor vaccinatie in aanmerking komen.
Voor de aK-vaccinatie geldt dat in het kader van het Rijksvaccinatieprogramma alleen kinderen die geboren zijn vanaf 1 januari 1998 en die de basisserie DKTP hebben voltooid voor vaccinatie in aanmerking komen.

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

1.7 Alle nadere regelingen welke met betrekking tot het Rijksvaccinatieprogramma 2002 worden getroffen, vereisen de goedkeuring van de Inspecteur-Generaal voor de Gezondheidszorg.

1.8 Exemplaren van deze folder kunnen worden aangevraagd bij de Inspectie voor de Gezondheidszorg, Postbus 16119, 2500 BC Den Haag, telefoon (070) 3405536.

2 ZUIGELINGEN en KLEUTERS

Vaccinatieschema

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

Op de leeftijd van respectievelijk **2, 3** en **4** maanden wordt één DKTP-vaccinatie gegeven. Er dient minimaal een periode van 4 weken in acht te worden genomen tussen de drie opeenvolgende vaccinaties. De vierde DKTP-vaccinatie wordt bij voorkeur gegeven op de leeftijd van 11 maanden. Er dient **tenminste een tussenperiode van 6 maanden** in acht te worden genomen tussen de derde DKTP-vaccinatie en de vierde DKTP-vaccinatie. Indien vaccinatie met 11 maanden binnen het reguliere programma niet goed mogelijk is, dan kan de vaccinatie met 12 maanden worden gegeven. Vaccinatie met 10 maanden is ongewenst.
Dosering: 1 ml INTRAMUSCULAIR.

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

Indien de kinkhoestvaccinatie gecontra-indiceerd is (zie R.J.F. Burgmeijer en D.J.A. Bolscher "Vaccinaties bij kinderen", 3e herziene druk, Van Gorcum 1998) en DTP in plaats van DKTP wordt gegeven, dient degene die de vaccinatie verricht dit **duidelijk** te vermelden op de oproepkaart die naar de entadministratie wordt gezonden. Er zijn overigens geen absolute contra-indicaties tegen de kinkhoestvaccinatie meer.

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

Op de leeftijd van respectievelijk **2, 3** en **4** maanden wordt één Hib-vaccinatie gegeven. Er dient minimaal een tussenperiode van 4 weken in acht te worden genomen tussen de drie opeenvolgende vaccinaties. De vierde Hib-vaccinatie wordt bij voorkeur op de leeftijd van 11 maanden gegeven. Er dient **tenminste een tussenperiode van 6 maanden** in acht te worden genomen tussen de derde Hib-vaccinatie en de vierde Hib-vaccinatie. Indien vaccinatie met 11 maanden binnen het reguliere programma niet goed mogelijk is, dan kan de vaccinatie met 12 maanden worden gegeven. Vaccinatie met 10 maanden is ongewenst.
Dosering: 0,5 ml INTRAMUSCULAIR.

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

- **BMR** (Buf - Mazelen - Rodehond)

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

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

De in 1998 geboren kinderen worden in 2002 gerevaccineerd met DTP-vaccin.
Dosering: 1 ml INTRAMUSCULAIR.

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

De in 1998 geboren kinderen worden in 2002 gerevaccineerd met aK-vaccin, maar uitsluitend indien zij al eerder een volledige serie DKTP-vaccinaties hebben ontvangen. Er wordt één vaccinatie gegeven. Indien kinderen geen (volledige) serie DKTP-vaccinaties hebben ontvangen, dient deze serie gegeven dan wel afgemaakt te worden.
Dosering: 0,5 ml INTRAMUSCULAIR (in de bovenarm).

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

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

Voor het afmaken van onvolledige series wordt verder verwezen naar R.J.F. Burgmeijer en D.J.A. Bolscher "Vaccinaties bij kinderen", 3e herziene druk, Van Gorcum 1998. Een nieuwe druk is in voorbereiding.

3 SCHOOLKINDEREN

Vaccinatieschema

De in 1990 geboren kinderen worden in 2002 gerevaccineerd met DTP-vaccin. Afhankelijk van de reeds vroeger gegeven vaccinaties worden 1, 2 of 3 vaccinaties gegeven.
Dosering: 1 ml INTRAMUSCULAIR.

De in 1993 geboren kinderen krijgen in 2002 een BMR-vaccinatie.
Dosering: 0,5 ml SUBCUTAAN.

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

4 SIMULTANE VACCINATIES EN REGISTRATIE VAN PARTIJNUMMERS

Simultane vaccinaties dienen altijd in verschillende ledematen te worden toegediend.

Indien simultane vaccinaties (zoals DKTP + Hib, DTP + BMR, DTP en aK) om een of andere reden niet simultaan worden gegeven, dient men tussen de vaccinaties de volgende intervallen aan te houden:
- een interval van tenminste 2 weken tussen de D(K)TP-, de Hib-, de DTP- en de aK-vaccinatie, ongacht de volgorde waarin ze worden gegeven.
- na een D(K)TP-vaccinatie, een Hib-vaccinatie en/of een aK-vaccinatie dient men 2 weken te wachten alvorens met BMR wordt gevaccineerd.
- na een BMR-vaccinatie dient men 4 weken te wachten alvorens men D(K)TP-, Hib- en/of aK-vaccin toedient.

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

Appendix 2 Package insert DPTP

RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEU

Difterie-, Kinkhoest-, Tetanus-, Poliomyelitisvaccin

Samenstelling

1 dosis (1 ml) bevat:

difterietoxoid	≥ 30	IE *
kinkhoestvaccin	4	IE
tetanustoxoid	≥ 60	IE
geinactiveerd poliovirus:		
type 1	40	DE **
type 2	8	DE
type 3	32	DE
aluminiumfosfaat	1,5	mg
2-fenoxyethanol	5	mg
formaldehyde	25	µg

*) IE = Internationale Eenheid
**) DE = D-antigeneenheden (eenheid voor poliocomponenten)

Farmaceutische vorm en presentatie

Difterie-, Kinkhoest-, Tetanus-, Poliomyelitisvaccin (DKTP) vaccin is een suspensie voor injectie en wordt afgeleverd in:
Fiolen à 1 ml (1 dosis) bestelnr. 260.1

Fabrikant en registratiehouder

RIVM, Postbus 1, 3720 BA Bilthoven
afd. verkoop SVM
Postbus 457, 3720 AL Bilthoven
Tel. 030-2748810

RVG nummer

DKTP vaccin is in het register ingeschreven onder RVG-nummer 17640.

Indicatie

Actieve immunisatie tegen difterie, kinkhoest, tetanus en poliomyelitis. Het vaccin wordt toegepast in het Rijksvaccinatieprogramma voor kinderen tot en met de leeftijd van 4 jaar.

Contra-indicaties

DKTP vaccin mag niet worden toegediend aan kinderen van wie aangetoond is dat ze allergisch zijn voor een of meerdere componenten van het vaccin.
Net als bij andere vaccins dient toediening van DKTP vaccin te worden uitgesteld als een kind aan een acute, ernstige, eventueel met koorts gepaard gaande ziekte lijdt. Een lichte infectie vormt echter geen contra-indicatie voor vaccinatie.

Speciale waarschuwingen en bijzondere voorzorgen bij gebruik

DKTP vaccin mag onder geen voorwaarde intravasculair worden toegediend.

Vaccinatie moet worden voorafgegaan door een beoordeling van de gezondheidstoestand van het kind (mede met betrekking tot eventuele bijwerkingen van eerdere vaccinaties) conform de instructies van het Rijksvaccinatieprogramma.

Indien na eerdere DKTP vaccinatie één of meerdere van de volgende verschijnselen optreedt: hoge koorts, aanhoudend, ontroostbaar huilen, collaps of een op shock gelijkende toestand (episoden van bleekheid, hypotonie en hyporesponsiviteit), convulsies (met of zonder koorts) kunnen volgende doses vaccins die de pertussis componenten bevatten in principe worden gegeven, maar kunnen aanvullende adviezen nodig zijn (bijvoorbeeld koortsverlaging).

Ook bij kinderen met progressieve neurologische aandoeningen, of bij kinderen bij wie na eerdere toediening van DKTP vaccin encefalopathie is gediagnosticeerd, dient de voordelen van verdere vaccinatie afgewogen te worden tegen de nadelen. In individuele gevallen zullen de voordelen vaak zwaarder wegen dan de mogelijke nadelen, zelfs wanneer er kinkhoest heerst.

Geen contra-indicatie zijn:
- een voorgeschiedenis van met koorts gepaard gaande convulsies en in de familie voorkomende idiopathische aanvallen
- besmetting met Human Immunodeficiency Virus (HIV).

Zoals bij alle injecteerbare vaccins dient te allen tijde adequate medische behandeling beschikbaar te zijn, voor het geval zich na toediening van het vaccin anafylactische reacties voordoen. Hiervoor dienen de instructies van het Rijksvaccinatieprogramma te worden gevolgd. Zonodig worden epinefrine injecties en corticosteroiden gegeven, gebaseerd naar leeftijd en/of lichaamsgewicht.

Voorzichtigheid dient te worden betracht bij het toedienen van DKTP vaccin aan kinderen met trombocytopenie of verhoogde bloedingsneiging, omdat bij hen na intramusculaire toediening bloedingen kunnen ontstaan.

Interacties met andere geneesmiddelen en andere vormen van interactie

DKTP vaccin kan gelijktijdig op verschillende injectieplaatsen worden toegediend met andere vaccins. Er zijn geen gegevens bekend over mogelijke interactie van DKTP- met BMR vaccin. Indien DKTP vaccin niet gelijktijdig met andere vaccins wordt gegeven, dient na een eerder gegeven geinactiveerd vaccin een interval van 2 weken, en na een eerder gegeven levend vaccin een interval van 4 weken in acht genomen te worden.

Dosering en wijze van toediening

Een dosis DKTP vaccin is 1 ml en dient diep intramusculair te worden gegeven. Een volledige immunisatie bestaat uit een primaire serie van drie DKTP entingen en een eerste revaccinatie. De primaire immunisatie van zuigelingen wordt gegeven vanaf de leeftijd van 2 maanden met een interval van tenminste een maand, en dient vóór de leeftijd van 6 maanden te zijn voltooid voor een optimale bescherming. De eerste revaccinatie ("DKTP-4") wordt toegediend 6 maanden na de laatste enting van de primaire serie gegeven. Met name ook prematuri geboren kinderen volgen dit schema weigens de kalenderleeftijd, zonder correctie voor de tijd vroeger geboorte. Dit schema wordt in het Rijksvaccinatieprogramma toegepast.

Indien de kleur van het vaccin duidelijk geel of violet is, mag het vaccin niet worden gebruikt. Vóór gebruik dient het vaccin te worden geschud. Na opschudden is het vaccin troebel.

Gebruik gedurende zwangerschap en het geven van borstvoeding

Geen bijzondere voorzorgen.

Bijwerkingen

Na toediening van DKTP vaccin kunnen lokale reacties optreden, die soms gepaard gaan met verschijnselen van algemene malaise en koorts. In zeldzame gevallen kan de kinkhoest component in het vaccin aanleiding geven tot een ernstige reactie zoals collaps of convulsie. Ook treedt sporadisch een toestand van encefalopathie na DKTP vaccinatie op, maar hierbij is een oorzakelijke relatie niet aannemelijk. Dergelijke complicaties worden waargenomen in een periode van 1 uur tot 3 dagen na enting. De meest ernstige reacties worden binnen 12 uur gezien. Artsen wordt verzocht mogelijke bijwerkingen te melden aan Afd. Klinisch Onderzoek van het Laboratorium Veldonderzoek Vaccins van het RIVM, tel. 030 - 274 24 24.

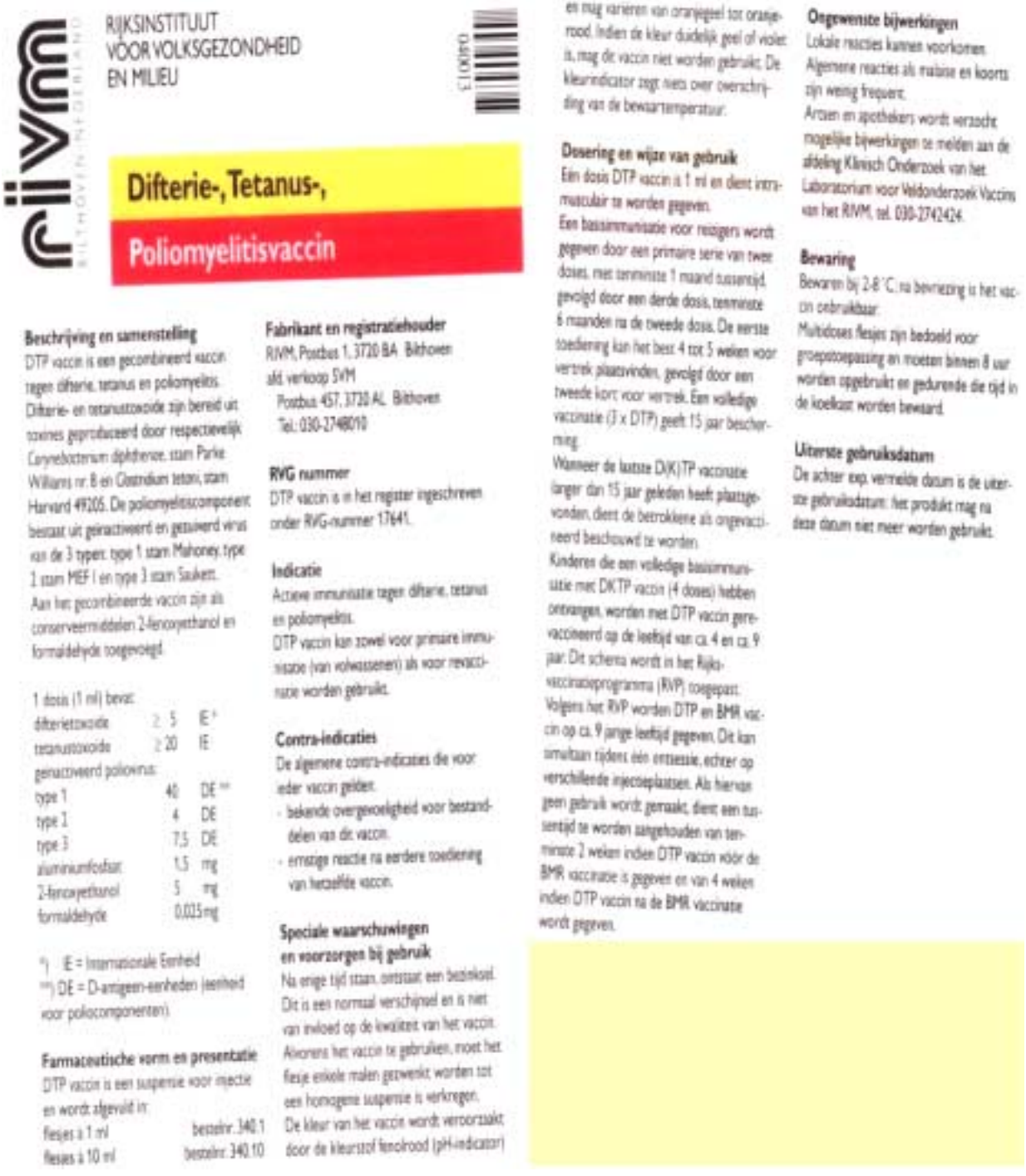
Bewaring

Bewaren bij 2-8 °C. Na bewaring is het vaccin onbruikbaar.

Uiterste gebruiksdatum

De datum achter "exp." en "niet te gebruiken na" is de uiterste gebruiksdatum.

Appendix 3 Package insert DTP



RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEU

0400 13

Difterie-, Tetanus-, Poliomyelitisvaccin

Beschrijving en samenstelling
DTP vaccin is een gecombineerd vaccin tegen difterie, tetanus en poliomyelitis. Difterie- en tetanustoxoide zijn bereid uit toxines geproduceerd door respectievelijk Corynebacterium diphtheriae, stam Parke Williams nr. 8 en Clostridium tetani, stam Harvard 49205. De poliomyeliscomponent bestaat uit geïnactiveerd en gezuiverd virus van de 3 typen: type 1 stam Mahoney, type 2 stam MEF I en type 3 stam Saukett.
Aan het gecombineerde vaccin zijn als conserveermiddelen 2-fenoxyethanol en formaldehyde toegevoegd.

1 dosis (1 ml) bevat:

difterietoxoide	≥ 5	IE *
tetanustoxoide	≥ 20	IE
geïnactiveerd poliovirus:		
type 1	40	DE **
type 2	4	DE
type 3	7,5	DE
aluminiumfosfaat	1,5	mg
2-fenoxyethanol	5	mg
formaldehyde	0,015	mg

*) IE = Internationale Eenheid
**) DE = D-antigeen-eenheden (eenheid voor poliocomponenten).

Farmaceutische vorm en presentatie
DTP vaccin is een suspensie voor injectie en wordt afgevuld in:

flesjes à 1 ml	bestelnr. 340.1
flesjes à 10 ml	bestelnr. 340.10

Fabrikant en registratiehouder
RIVM, Postbus 1, 3720 BA Bilthoven
afd. verkoop SVM
Postbus 457, 3720 AL Bilthoven
Tel.: 030-2748010

RVG nummer
DTP vaccin is in het register ingeschreven onder RVG-nummer 17641.

Indicatie
Actieve immunisatie tegen difterie, tetanus en poliomyelitis.
DTP vaccin kan zowel voor primaire immunisatie (van volwassenen) als voor revaccinatie worden gebruikt.

Contra-indicaties
De algemene contra-indicaties die voor ieder vaccin gelden.
- bekende overgevoeligheid voor bestanddelen van dit vaccin.
- ernstige reactie na eerdere toediening van hetzelfde vaccin.

Speciale waarschuwingen en voorzorgen bij gebruik
Na enige tijd staan, ontstaat een bezinksel. Dit is een normaal verschijnsel en is niet van invloed op de kwaliteit van het vaccin. Alvorens het vaccin te gebruiken, moet het flesje enkele malen geschud worden tot een homogene suspensie is verkregen.
De kleur van het vaccin wordt veroorzaakt door de kleurstof fenolrood (pH-indicator) en mag variëren van oranjegeel tot oranjerood. Indien de kleur duidelijk geel of violet is, mag dit vaccin niet worden gebruikt. De kleurindicator zegt niets over overschrijding van de bewaartemperatuur.

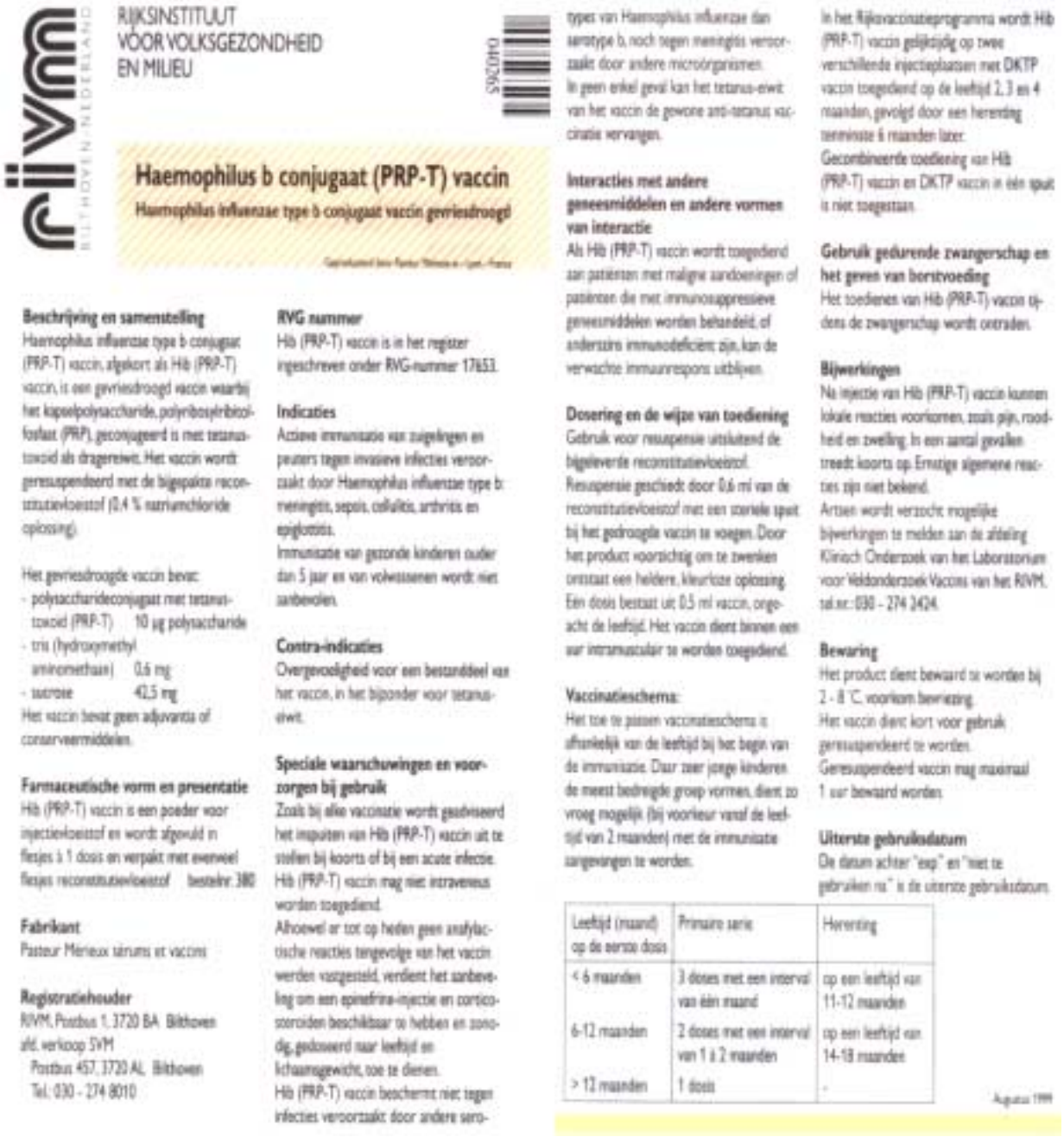
Dosering en wijze van gebruik
Een dosis DTP vaccin is 1 ml en dient intramusculair te worden gegeven.
Een basisimmunisatie voor reizigers wordt gegeven door een primaire serie van twee doses, met tenminste 1 maand tussentijd, gevolgd door een derde dosis, tenminste 6 maanden na de tweede dosis. De eerste toediening kan het best 4 tot 5 weken voor vertrek plaatsvinden, gevolgd door een tweede kort voor vertrek. Een volledige vaccinatie (3 x DTP) geeft 15 jaar bescherming.
Wanneer de laatste D(K)TP vaccinatie langer dan 15 jaar geleden heeft plaatsgevonden, dient de betrokkene als ongevaccineerd beschouwd te worden.
Kinderen die een volledige basisimmunisatie met D(K)TP vaccin (4 doses) hebben ontvangen, worden met DTP vaccin gerevaccineerd op de leeftijd van ca. 4 en ca. 9 jaar. Dit schema wordt in het Rijksvaccinatieprogramma (RVP) toegepast.
Volgens het RVP worden DTP en BMR vaccin op ca. 9 jarige leeftijd gegeven. Dit kan simultaan tijdens één entsessie, echter op verschillende injectieplaatsen. Als hiervan geen gebruik wordt gemaakt, dient een tussentijd te worden aangehouden van tenminste 2 weken indien DTP vaccin vóór de BMR vaccinatie is gegeven en van 4 weken indien DTP vaccin na de BMR vaccinatie wordt gegeven.

Ongewenste bijwerkingen
Lokale reacties kunnen voorkomen.
Algemene reacties als malaise en koorts zijn weinig frequent.
Artsen en apothekers wordt verzocht mogelijke bijwerkingen te melden aan de afdeling Klinisch Onderzoek van het Laboratorium voor Veldonderzoek Vaccins van het RIVM, tel. 030-2742424.

Bewaring
Bewaren bij 2-8 °C, na bevriezing is het vaccin onbruikbaar.
Multidoses flesjes zijn bedoeld voor groepstoepassing en moeten binnen 8 uur worden opgebruikt en gedurende die tijd in de koelkast worden bewaard.

Uiterste gebruiksdatum
De achter exp. vermelde datum is de uiterste gebruiksdatum: het produkt mag na deze datum niet meer worden gebruikt.

Appendix 4 Package insert Hib



RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEU

SYSTEMO

Haemophilus b conjugaat (PRP-T) vaccin

Haemophilus influenzae type b conjugaat vaccin gevriesdroogd

Beschrijving en samenstelling
Haemophilus influenzae type b conjugaat (PRP-T) vaccin, afgekort als Hib (PRP-T) vaccin, is een gevriesdroogd vaccin waarbij het kapselpolysaccharide, polyribosylribitolfosfaat (PRP), geconjugeerd is met tetanustoxoid als dragereiwit. Het vaccin wordt geresuspendeerd met de bijgeleverde reconstitutievloeistof (0,4 % natriumchloride oplossing).

Het gevriesdroogde vaccin bevat:
- polysaccharideconjugaat met tetanustoxoid (PRP-T) 10 µg polysaccharide
- tris (hydroxymethyl aminomethaan) 0,6 mg
- sucrose 42,5 mg

Het vaccin bevat geen adjuvantia of conserveermiddelen.

Farmaceutische vorm en presentatie
Hib (PRP-T) vaccin is een poeder voor injectievloeistof en wordt afgevuld in flesjes à 1 dosis en verpakt met eveneel flesjes reconstitutievloeistof bestelnr. 380

Fabrikant
Pasteur Mérieux sérums et vaccins

Registratiehouder
RIVM, Postbus 1, 3720 BA Bilthoven
afd. verkoop SVM
Postbus 457, 3720 AL Bilthoven
Tel.: 030 - 274 8010

RVG nummer
Hib (PRP-T) vaccin is in het register ingeschreven onder RVG-nummer 17653.

Indicaties
Actieve immunisatie van zuigelingen en peuters tegen invasieve infecties veroorzaakt door Haemophilus influenzae type b: meningitis, sepsis, cellulitis, arthritis en epiglottitis.
Immunisatie van gezonde kinderen ouder dan 5 jaar en van volwassenen wordt niet aanbevolen.

Contra-indicaties
Overgevoeligheid voor een bestanddeel van het vaccin, in het bijzonder voor tetanuseiwit.

Speciale waarschuwingen en voorzorgen bij gebruik
Zoals bij alle vaccinatie wordt geadviseerd het inspuiten van Hib (PRP-T) vaccin uit te stellen bij koorts of bij een acute infectie.
Hib (PRP-T) vaccin mag niet intraveneus worden toegediend.
Alhoewel er tot op heden geen anafylactische reacties tengevolge van het vaccin werden vastgesteld, verdient het aanbeveling om een epinefrine-injectie en corticosteroiden beschikbaar te hebben en zonodig, gedoseerd naar leeftijd en lichaamsgewicht, toe te dienen.
Hib (PRP-T) vaccin beschermt niet tegen infecties veroorzaakt door andere serotypes van Haemophilus influenzae dan serotype b, noch tegen meningitis veroorzaakt door andere microörganismen.
In geen enkel geval kan het tetanus-eiwit van het vaccin de gewone anti-tetanus vaccinatie vervangen.

Interacties met andere geneesmiddelen en andere vormen van interactie
Als Hib (PRP-T) vaccin wordt toegediend aan patiënten met maligne aandoeningen of patiënten die met immunosuppressieve geneesmiddelen worden behandeld, of anderszins immunodeficiënt zijn, kan de verwachte immuunrespons uitblijven.

Dosering en de wijze van toediening
Gebruik voor resuspensie uitsluitend de bijgeleverde reconstitutievloeistof.
Resuspensie geschiedt door 0,6 ml van de reconstitutievloeistof met een steriele spuit bij het gedroogde vaccin te voegen. Door het product voorzichtig om te zwenken ontstaat een heldere, kleurloze oplossing.
Eén dosis bestaat uit 0,5 ml vaccin, ongeacht de leeftijd. Het vaccin dient binnen een uur intramuscular te worden toegediend.

Vaccinatieschema:
Het toe te passen vaccinatieschema is afhankelijk van de leeftijd bij het begin van de immunisatie. Daar zeer jonge kinderen de meest bedreigde groep vormen, dient zo vroeg mogelijk (bij voorkeur vanaf de leeftijd van 2 maanden) met de immunisatie aangevangen te worden.

Leeftijd (maand) op de eerste dosis	Primaire serie	Herenting
< 6 maanden	3 doses met een interval van één maand	op een leeftijd van 11-12 maanden
6-12 maanden	2 doses met een interval van 1 à 2 maanden	op een leeftijd van 14-18 maanden
> 12 maanden	1 dosis	-

In het Rijksvaccinatieprogramma wordt Hib (PRP-T) vaccin gelijktijdig op twee verschillende injectieplaatsen met DKTP vaccin toegediend op de leeftijd 2, 3 en 4 maanden, gevolgd door een herenting tenminste 6 maanden later.
Gecombineerde toediening van Hib (PRP-T) vaccin en DKTP vaccin in één spuit is niet toegestaan.

Gebruik gedurende zwangerschap en het geven van borstvoeding
Het toedienen van Hib (PRP-T) vaccin tijdens de zwangerschap wordt ontraden.

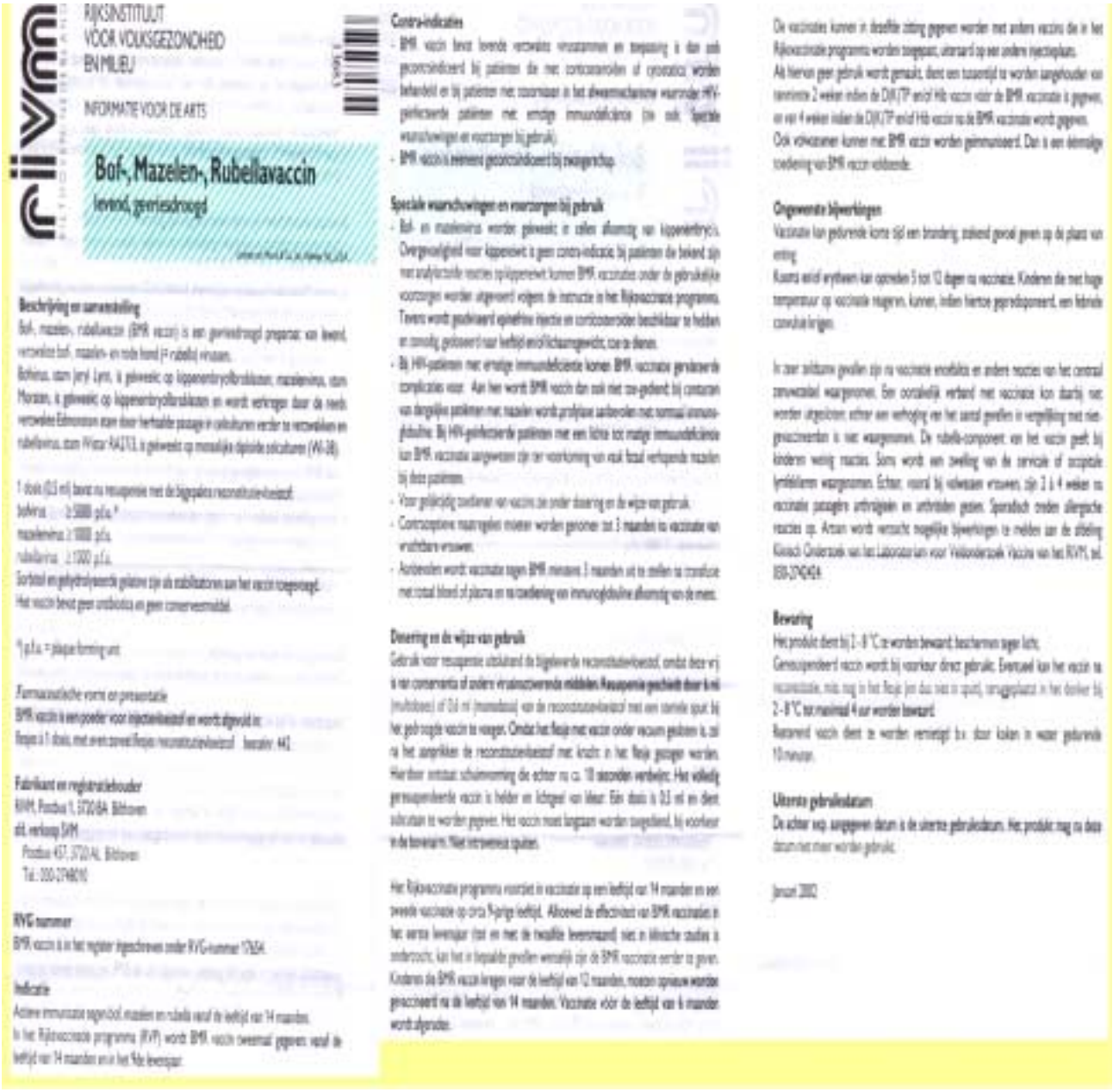
Bijwerkingen
Na injectie van Hib (PRP-T) vaccin kunnen lokale reacties voorkomen, zoals pijn, roodheid en zwelling. In een aantal gevallen treedt koorts op. Ernstige algemene reacties zijn niet bekend.
Artsen wordt verzocht mogelijke bijwerkingen te melden aan de afdeling Klinisch Onderzoek van het Laboratorium voor Veldonderzoek Vaccins van het RIVM, tel.nr.: 030 - 274 2424.

Bewaring
Het product dient bewaard te worden bij 2 - 8 °C, voorkom bevriezing.
Het vaccin dient kort voor gebruik geresuspendeerd te worden.
Geresuspendeerd vaccin mag maximaal 1 uur bewaard worden.

Uiterste gebruiksdatum
De datum achter "exp." en "niet te gebruiken na:" is de uiterste gebruiksdatum.

Augustus 1999

Appendix 5 Package insert MMR



RIJKSINSTITUUT
VOOR VOLKSGEZONDHEID
EN MILIEU

INFORMATIE VOOR DE ARTS

Bof-, Mazelen-, Rubellavaccin
levend, gevriesdroogd

Beschrijving en samenstelling

Farmaceutische vorm en presentatie

Fabrikant en registratiehouder

RVG nummer

Indicatie

Contra-indicaties

Speciale waarschuwingen en voorzorgen bij gebruik

Dosering en de wijze van gebruik

Bewaring

Uiterste gebruiksdatum

Januari 2002

Appendix 6 Package insert aK

GlaxoSmithKline INFORMATIE VOOR DE OUDERS OF VERZORGERS

GlaxoSmithKline INFORMATIE VOOR DE ARTS

Acellulair kinkhoestvaccin

Acellulair kinkhoestvaccin

Appendix 7 Package insert MenC

NeisVac-C™

Patiëntenbijsluiter

Baxter

Lees deze bijsluiter zorgvuldig door voordat u start met het gebruik van dit geneesmiddel.

- Bewaar deze bijsluiter, het kan nodig zijn om deze nogmaals door te lezen.
- Heeft u nog vragen, raadpleeg dan uw arts of apotheker.
- [illegible]

Inhoud van deze bijsluiter

1. Wat is NeisVac-C™ en waarvoor wordt het gebruikt ?
2. Wat u moet weten voordat u NeisVac-C™ krijgt toegediend
3. Hoe wordt NeisVac-C™ toegediend ?
4. Mogelijke bijwerkingen
5. Hoe bewaart u NeisVac-C™ ?

NeisVac-C™, suspensie voor injectie in een voorgevulde spuit

Geconjugeerd meningokokken-C-polysacharide vaccin (geadsorbeerd)

[illegible]

Andere belangrijke informatie

[illegible]

3. Hoe wordt NeisVac-C™ toegediend ?

[illegible]

1. Wat is NeisVac-C™ en waarvoor wordt het gebruikt ?

[illegible]

2. Wat u moet weten voordat u NeisVac-C™ krijgt toegediend

Gebruik NeisVac-C™ niet,

[illegible]

Wees extra voorzichtig met NeisVac-C™,

[illegible]

4. Mogelijke bijwerkingen

[illegible]

Zwangerschap

[illegible]

Borstvoeding

[illegible]

Rijvaardigheid en het gebruik van machines

[illegible]

Belangrijke informatie over bepaalde bestanddelen van NeisVac-C™

[illegible]

Gebruik van NeisVac-C™ in combinatie met andere geneesmiddelen

[illegible]

5. Hoe bewaart u NeisVac-C™ ?

[illegible]

Uiterste gebruiksdatum

[illegible]

Deze bijsluiter is voor het laatst herzien/goedgekeurd in

[illegible]