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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 is done in close collaboration with the National Health Council. Reports from Health Care workers are received mainly by telephone through the operating vaccine information and advisory service. Further data are obtained, if necessary, from parents, general practitioners, paediatricians etc. After supplementation and verification of data a (working) diagnosis is made and causality assessed. In this report on 1999 an overview of all received AEFI is presented with classification according to case definitions and causality. Reporting bias, background rates of specific events and possible pathophysiology of symptoms are discussed. On a total of approximately 2 million vaccinations 1197 AEFI were submitted. Of these 1% (12) was unclassifiable because of missing information. In 84% (996) of the classifiable events a possible causal relation with vaccination was established and in 16% (189) the events were judged to be coincidental. Compared with 1998 there was again a rise in the number of notifications. This is probably attributable to the elevated number of vaccinated infants due to the change to an accelerated schedule from March 1999 onwards.

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Abbreviations

AE	Adverse Event
AEFI	Adverse Event Following Immunisation (melding of postvaccinale gebeurtenis)
AR	Adverse Reaction (bijwerking)
BCG	Bacille Calmette Guérin (vaccine)
BHS	Breath Holding Spell
BMR	Bof Mazelen Rodehond vaccin (MMR)
CB	Child Health Clinic (consultatiebureau)
CBS	Statistics Netherlands
CIE	Centre for Infectious diseases Epidemiology (of RIVM)
DM	Diabetes Mellitis
DKTP	Difterie Kinkhoest Tetanus Polio vaccin (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 (huisarts)
GR	Health Council (Gezondheidsraad)
HepB	Hepatitis B (vaccine)
HBIg	Hepatitis B Immunoglobulin
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HHE	Hypotonic Hyporesponsive Episode (collapse)
Hib	Haemophilus influenzae type b (vaccine)
IGZ	Inspectorate of Health Care
IPV	Inactivated Polio Vaccine
ITP	Idiopathic Thrombocytopaenic Purpura
JGZ	Child Health Care (jeugdgezondheidszorg)
LAREB	Netherlands Pharmacovigilance Foundation
LVO	Laboratory for Clinical Vaccine Research (of RIVM)
MAE	Medical Consultant of PEA
MMR	Measles Mumps Rubella vaccine
PEA	Provincial Immunisation Administration
PMS	Post Marketing Surveillance
PRP-T	Polyribosil Ribitol Phosphate Tetanus conjugate vaccine
RIVM	National Institute of Public Health and Environment
RVP	National Vaccination Programme
SVM	Foundation for the Advancement of Public Health and Environmental Protection
TBC	Tuberculosis
WHO	World Health Organisation

Contents

Samenvatting

Vermoede bijwerkingen van vaccinaties van het Rijksvaccinatieprogramma (RVP) worden in Nederland centraal geregistreerd 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. 96% van de spontane meldingen komt telefonisch binnen, in hoofdzaak vanuit de Jeugdgezondheidszorg (81%). Nadere gegevens van anderen dan de melder, bijvoorbeeld van ouders, huisarts of ziekenhuis worden in circa 67% 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. Door aanpassing van de werkwijze is er hierin een afname in aantal geweest in 1996. 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 zesde jaarrapport.

In 1999 zijn 1197 meldingen binnengekomen, betreffende 1142 kinderen, op een totaal van meer dan 2 miljoen vaccinaties per jaar. 12 meldingen (1%) waren niet te beoordelen wegens het ontbreken van informatie. 84% (996) van de meldingen werd als bijwerking beoordeeld met een mogelijk, waarschijnlijk of zeker causaal verband. Een toevallige samenloop werd aangenomen in 16% (189) van de meldingen.

Van de milde, zogenaamde "minor", algemene, huid- of lokale verschijnselen (524) werden 393 (75%) meldingen als mogelijke bijwerking uitgeboekt in 1999.

Verkleurde benen (in 1995 voor het eerst afgesplitst van de huidverschijnselen) werden 130 keer gemeld, met in op twee na alle gevallen een mogelijke causale relatie.

Andere zogenaamde "major" postvaccinale gebeurtenissen (gerubriceerd onder convulsies, collaps, “ziek major”, lokaal major, persistent screaming en de sterfgevallen) werden 536 keer gemeld en in 88% (473) beoordeeld als mogelijke bijwerking. Collaps, waaronder ook atypische en onvolledige episodes, werd 221 maal gediagnosticeerd, met slechts in acht gevallen geen oorzakelijk verband en een keer niet te beoordelen. Daarnaast enkele keren Breath-Holding-Spells (5) en flauwvallen (18) in oudere kinderen. In 1999 werden 77, convulsies gemeld, waarvan zes afebriel, die in 71 gevallen (92%) als mogelijke bijwerking werden beoordeeld. De 43 atypische aanvallen hadden in 86% (37) een mogelijk causaal verband. Epilepsie (3) werd niet als bijwerking beoordeeld, maar als een coïncidentie. Alle meldingen van persistent screaming (34) werden gezien als bijwerking. Koorts van $\geq$40,5°C was de werkdiagnose bij 57 kinderen uit de “ziek major” groep, op een na allemaal beschouwd als bijwerking. Van de 54 andere beelden uit de “ziek major” groep was er 21 keer een mogelijk causaal verband, heftig huilen (4), vaccinitis (5) myoclonieën (1), rilling (1), geprikkeld gedrag (1), in op een na met ook zeer hoge koorts. Daarnaast was er in de

"ziek major" groep nog uitdroging (2), apneu (2), en ITP (4) en ontregeling van een stofwisselingsziekte (1). De overige 33 meldingen waren coïncidenteel. Er waren 11 abcessen, waarvan slechts een gekweekt (negatief), en 11 anderszins heftige lokale reacties in een geval niet te beoordelen. De zeven sterfgevallen in 1999 gemeld, zijn na uitgebreide evaluatie vier keer als toevallige samenloop beoordeeld en een keer als niet te beoordelen gerubriceerd hoewel oorzakelijk verband onwaarschijnlijk werd geacht. Twee kinderen overleden na DKTP/Hib vaccinaties waarbij er mogelijk een (indirect) verband bestond met de vaccinaties. Het betrof een kind met mogelijke ontregeling van een tevoren niet onderkende stofwisselingsstoornis en een kind met een inoperabel ernstig aangeboren hartgebrek.
De meeste meldingen betroffen simultane DKTP en Hib vaccinaties (954). BMR was betrokken in 179 van de meldingen, waarvan 39 maal gecombineerd met andere vaccins. In 63% was er een mogelijke causale relatie met de BMR. Voor de andere vaccin(combinatie)s was dit percentage 84%. Vergeleken met 1998 was er een stijging van het aantal meldingen van 9%. Deze toename gold alleen de simultane DKTP en Hib vaccinaties. Deze stijging kan verklaard worden door de vervroeging van het vacinatieschema, met als gevolg een toegenomen aantal gevaccineerde kinderen in 1999 en mogelijk ook verhoogde aandacht, toegenomen vragen en onzekerheid. Daarnaast kan er ook enige werkelijke toename van bijwerkingen zijn na DKTP/Hib vaccinaties en/of een verschuiving binnen de verschillende doses, met name van leeftijdspecifieke beelden als collaps en verkleurde benen. Nadere analyse daarvan kan pas plaatsvinden bij het beschikbaar worden van precieze getallen over de aantallen gevaccineerde kinderen en na het voltooien van de vaccinatieserie van een volledig geboortecohort.

Summary

Adverse Events Following Immunisation (AEFI) under the Netherlands Vaccination Programme (RVP) have been monitored by the National Institute of Public health and 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. 96% of reports come in by telephone, in majority from Child health Clinic staff (81%). Parents, GP's and/or hospital provided additional data on request (67% of cases). After supplementation and verification of data RIVM makes a (working) diagnosis and assesses causality. 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 the latter cases and the aggregated results of the other ones 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 fifth annual report.

In 1999, on a total of over 2 million vaccinations, 1197 AEFI were submitted, concerning 1042 children. Of these only 1% (12) were not classifiable because of missing information. 84% (996) of classifiable events were judged to be possibly, probably or definitely causally related with the vaccination and 16% (189) of the events were coincidental.

So-called "minor" skin, local or systemic events were registered in 524 cases of which 393 (75%) were classified as possible adverse reactions.

Discoloured legs were reported 130 times with a causal relation more or less likely in all but two cases. Other so-called "major" adverse events (categorised under convulsions, collapse, persistent screaming, general major illness and death) occurred in 536 cases of which 88% (473) were possible adverse reactions. Collapse, including atypical and incomplete episodes, was diagnosed 221 times, in eight cases without causal relation and once non-classifiable. Five times breath holding spells and 18 times fainting in older children were reported. Convulsions were diagnosed in 77 cases, of which six were non-febrile, with in 92% (71) inferred causality. Atypical attacks were diagnosed 43 times, of which 86% (37) with a possible causal relation. Epilepsy (3) was not considered causally related with the vaccinations. All of the 34 persistent screaming cases were considered adverse reaction. Fever $\geq$40.5°C was the working diagnosis in 57 cases of the major illness group, in all but one with inferred causality. Of the other 54 major illness cases 21 had a possible causal relation: fierce crying (4), "vaccinitis" (5), myoclonics (1), chills (1), irritability (1), in all but one case with very high fever. Also dehydration (2), ITP (4), apnoea (2) and derangement of metabolic disorder (1). The other 33 were considered to be unrelated. There were 11 abscesses, only once cultured (negative), and 11 other major local reactions, once non-classifiable. After thorough assessment were four of the seven death cases considered as chance occurrences with other causes. Once the case was considered non-classifiable but

causal relation was judged to be unlikely. Two children died following DPTP/Hib vaccinations with possible (indirect) causal relation with the vaccinations. One child had possibly derangement of previously unrecognised metabolic disorder and one child had a severe inoperable congenital heart malformation.
Most frequently reports involved DPTP and Hib vaccination (954). MMR was involved 179 times, 39 times with simultaneous other vaccines. In 63% of cases there was a possible causal relation with MMR. For the other vaccine combinations this percentage was 84%. Compared to 1998 the number of reports rose with 9%. This concerned only the simultaneous DPTP/Hib vaccinations. This increase could be caused by the change in schedule with a higher number of children vaccinated in 1999 and also possibly increased awareness, apprehension and consultation. Also there could be some true increase in certain adverse events and/or change in distribution over the different vaccine doses, especially with age specific events as collapse and discoloured legs. Thorough evaluation is only possible when population statistics and vaccination coverage have been made available and only after a full birth cohort has participated in the new accelerated vaccination schedule however.

1. Introduction

Identification, registration, and assessment of adverse events following drug-use are important aspects of post marketing research. 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 of Public Health and Environment (RIVM) has the task of monitoring 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 issue of the RVP. By their nature they do not permit comparing rates and nature 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 1999 report contains a description of the procedures for soliciting notifications, verification of symptoms, diagnosis according to case definitions, and causality assessment. Notifications were followed with special attention this year for a change in schedule was adopted for the birth cohorts of 1999 and later. The primary doses of DPTP/Hib were moved ahead by one month, resulting in start of the programme at two months of age.
We will discuss some specific adverse events and their relation to the vaccination. Special attention will be given to underreporting and to prevention of adverse events and contra-indications. This RIVM report on adverse events is only issued in English. 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).

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 a task of the National Institute of Public Health and Environment (RIVM): the safety surveillance by the Laboratory for Clinical Vaccine Research (LVO) and the surveillance of effectiveness the Centre for Infectious Disease Epidemiology (CIE) [2].

Requirements for post marketing surveillance of adverse reactions 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 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.

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 [7,8]. Not only true side effects but also events with only a temporal association with the vaccination may jeopardise uptake of the vaccination programme [9]. This has been exemplified in Sweden, in the United Kingdom and in Japan in the seventies and eighties. 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 [10]. But also recently anxiety about safety rather than actual associations caused cessation of the hepatitis B programme in France [11,12]. Even at this moment the uptake of MMR in the UK is very much under pressure because of unfounded allegations about association of the vaccine with autism and inflammatory bowel disease [7,13,14,15,16,17,18,19,20].

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 reassesses the more serious events presented by RIVM. The GR advises the Minister of Health on the safety of the Vaccination Programme with annual reports [21]. 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 [22,23,24,25,26,27]. 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.

3. The National 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 [28,29]. At first mono-vaccines against diphtheria, tetanus and pertussis were used and the combined DTP 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 1999 is included in box 1 (appendix 2).
From this year on the programme has an earlier start, at two months in stead of three. This was decided upon because of the resurgence of pertussis in the Netherlands in order two achieve protection as early as possible for the youngest, most vulnerable children. 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[30].

Box 1. Schedule of the National Vaccination Programme of the Netherlands in 1999

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

DPTP, DTP and MMR are produced by SVM/RIVM; Hib (PRP-T) vaccine is produced by SVM/Pasteur-Merieux (see appendix 3-7). BCG vaccination is not included in the RVP. Vaccination is offered only to children with higher risk of acquiring tuberculosis when travelling to or staying in countries with a high prevalence. Usually vaccination takes place in the second half-year of life [28]. Hepatitis B vaccination (HepB) is available for children of HBsAg positive mothers. This vaccination is given, following HBIg administration at birth, in a four 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 [28].
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 temporary reduced supply MMR from a different manufacturer has been used in the RVP in 1999 and 2000. See appendix 7.

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) [28,29]. 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) guards and promotes 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 reimbursement 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 an 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.
The PEA databases also contain results of heel prick tests and of prenatal hepatitis B screening and subsequent vaccinations.

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 [31]. 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 and congenital hypothyroidism (PKU/CHT). 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.
In the first year of life 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. Intervals 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 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 and Hib is over 97% with a slightly lower uptake for MMR of 95% [32]. (Accurate numbers on birth cohorts 1997, 1998 and 1999 have not yet been made available by IGZ)

3.4 Safety Surveillance

Since 1962 an adverse event (AE) surveillance system for the National Vaccination Programme (RVP) has been in effect. It is an enhanced passive reporting system including a 24 hours 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 mail or fax.
The annually distributed vaccination programme (appendix 2) by the Inspectorate of Health Care (IGZ) encourages Health Care providers to report adverse events to LVO-RIVM, giving address, telephone number and fax number. These are also mentioned on the package inserts of the vaccines (appendix 3-6). Most municipal and regional Child Health organisations, which provide the vast majority of vaccinations, have explicit guidelines for notifying AE to LVO-RIVM. The countrywide used guideline book on the RVP with background, execution and procedures, contains a (LVO-RIVM written) chapter on possible side effects and gives ample information on notification procedures [28]. LVO-RIVM promotes reporting through information, education and publications, for instance by contributing to refresher courses for Child Health Clinic staff. Family physicians and paediatricians are informed at symposia and lately also 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 or, Health Care providers or may lead to adverse publicity. Events that lead to deferral or cessation of further vaccinations are considered as serious and therefore should be reported, too (see box 2).

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 LVO-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 LVO-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 LVO-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 LVO-RIVM [21]. 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, LVO-RIVM makes an annual report on adverse events and no longer reports indirectly via reports by GR. For further details see paragraph 5.7.

4. Materials

4.1 Post Vaccination Events

Events following immunisations do not necessarily have a causal relation with the vaccination and some have a temporal association only and are in fact mere coincidental[8,33]. 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; in general only events within 28 days of vaccination are regarded as potential side effects. For some disease entities a longer 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 Immunisations (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: an adverse event with a presumed, supposed or assessed causal relation with the 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)[34,35].

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.
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. 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 (see box 4). 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

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
cluster reports single, multiple or compound	one vaccination date and/or one set of vaccines or badges or one age group or one provider or area

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 about the likelihood of a causal relation between vaccination and event and given advice on subsequent vaccinations. A formal written assessment is made of severe events and usually also of "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.

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 health clinic staff. They have the chart of the child ready for this purpose. In the case of incomplete records or severe, complex or difficult to interpret events, the involved family physician and hospital staff are contacted. In case of anxiety, confusion or missing data, a full history is also taken from the parents who are asked to provide a detailed description of the adverse event and circumstances. This interview is mostly taken by telephone but sometimes a physician of LVO-RIVM visits parents at home or at the local Clinic.

5.3 Working Diagnosis

After verification and completion of data a diagnosis is made. If the 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 is discussed in the periodic clinical conference of the physicians of LVO-RIVM. 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 [34]. This requires

adequate knowledge of epidemiology, child health, immunology, etiology 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. For different (nature of) side effects different time limits/risk time may be applied. Causal relation will then be appraised on the basis of a checklist, resulting in an indication of the probability/chance 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.
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*.

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

Generally also is considered to what extend the vaccine or vaccination has contributed to the event and how. This is especially important in case faulty procedures are involved. 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, from 1995 onwards, for the purpose of aggregated analysis. Formerly these events were either classified under skin symptoms or under local reactions (see also box 7). For classification case definitions are used.

- 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. 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.
- General skin symptoms: skin symptoms that are not general (rash) illness and not considered extensions of a local reaction fall in this category. Like exanthema or other rashes as erythema, urticaria, that are not restricted to the injection site. Also circumscript lesions distant from the injection site, are included and the harlequin syndrome is booked under skin symptoms as well. Also some mild common 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 legs and/or leg petechiae, with or without swelling. Extensive local reactions are not included.

- Faints: Collapse reactions (HHE), a sudden loss of consciousness, loss of muscle tone and pallor, 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, annotation will be made also. 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 also listed as a separate group within this category. Just pallor or apathy or prolonged sleeping or limpness 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 ≥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 phenomena 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. 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 intracranial 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		disease entity with diffuse or patchy discoloration of legs not restricted to injection site and/or leg petechiae
faints		collapse with pallor or cyanosis, limpness and loss of consciousness; included are also fainting and breath holding spells.
fits		seizures with or without fever, epilepsy or atypical attacks that could have been seizures
encephalitis/encephalopathy		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		life threatening circulatory insufficiency in close connection with intake of allergen, with or without laryngeal oedema or bronchospasm.
death		any death following vaccination irrespective of cause

5.6 Recording, Filing and Feedback

Symptoms, (working) diagnosis, event category and assessed causal relation are recorded on the notification file together with all other information about the child, as medical history or discharge letters. Severe and other important events are discussed in the periodic clinical conference among the physicians of LVO-RIVM, before final assessment, critical 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 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 on the case, there is a reassessment also 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 are as a rule 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. In time, computer generated 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. A project has been started for a database application, which 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 LVO-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 LVO-RIVM, the final judgement on the safety of the programme is reached. Physicians of LVO-RIVM are advisory members of this GR committee. Annually, GR makes a working visit to LVO-RIVM to audit the proper procedures and the completeness of registration and the quality and consistence of assessments.
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 LVO-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 (1998) this change in procedure did have impact on the number of written reports by LVO-RIVM and reassessed cases by GR. The GR committee however, considered all the aggregated results and this current report will be commented upon in their combined evaluation over five years.

5.8 Annual Reports and Aggregated Analysis

The coded forms are used as data sheets for the annual reports. For 1998 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 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 has been an independent external inspection and the GR audit over the year 1998. This will be commented upon in the combined GR report over 1996-1999.

6. Results

6.1 Number of Reports

In 1999 LVO-RIVM received 1189 notifications of adverse events, on a total of over 2 million vaccinations. (Birth cohort 1998, 199.408 and 1999, 201.000; CBS per may 2000) Eight notifications were compound with two distinct adverse events concerning one vaccination date. This annual report thus contains 1197 reported adverse events.
These reports involve 1142 children. There were 44 children with multiple reports, of which three concerned three different vaccination dates and once one of the double reports was also compound. Multiple and compound reports are listed under the respective event categories. In 1998 there were 26 multiple reports and nine compound reports. 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. Types of reports of notified AEFI in 1999

notifications	children	adverse events
single	1091	1091[b]
multiple	43[a]	89
compound	7	14
compound and multiple	1	3
total	1142	1197

[a] three times triple report
[b] 20 times multiple reports in previous or following years

From 1994 onwards comparisons of notifications are valid because the criteria for recording have been consistent, criteria for events eligible for written assessments have changed however. The number of advised vaccines has not changed since medio 1993, but the birth cohort has gradually increased by approximately 5%. (see paragraph 6.3 on reporting rates)

Table 2. Number of reported AEFI per year

year of notification	written assessments[a]	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

[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

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). 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 and possibly to some increase in actual adverse reactions as well [25]. (See report on 1998, 000001 004, www.rivm.nl)
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.
As in previous years the notification rate is not even over the months, range 82-123, with again the lowest rate in January and December.

6.2 Reporters

The first person to notify LVO-RIVM about an adverse event is the reporter. As in previous years the vast majority of reports were made by telephone (table 3). Only 46 (3.8%) 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 or fax. Over the last six years the number of written notifications fluctuates a little between 25 en 51. Reports from Child Health Clinics accounted for 79% of the total number with a stabilised share of reports by the nurse.

Table 3. Source and reporting route of AEFI in 1994-1999

		1994	1995	1996	1997	1998	1999	tel.	mail
Clinic staff*	Physician	474	548	466	547	678	722	690	32
	Nurse	78	102	116	142	219	221	221	-
Paediatrician		60	59	56	39	69	70	65	5
General Practitioner		25	13	26	20	35	34	32	2
School Health Service		15	18	17	10	31	27	27	-
District Consultant		9	18	11	16	15	16	12	4
Parent		25	34	35	40	52	91	89	2
Other		5	6	2	7	1	9#	8	1
Unknown		21	2	3	1	-	7	7	-
Total		712	800	732	822	1100	1197	1151	46

* including staff of refugee clinics
\# pharmacist (3), laboratory (4), anti-vaccine-movement consultant (1), lareb (1)

The parents of 91 (7.6%) children reported directly themselves; mostly they were advised to do so by the clinic staff. This percentage of parent reports is higher than in previous years (around 4.8%). Absolute numbers are increasing from 1994 onwards. The other notification sources were more or less stable. We failed to note the reporting source in 7 cases. See also paragraph 6.6 for information sources.

6.3 Regional Distribution

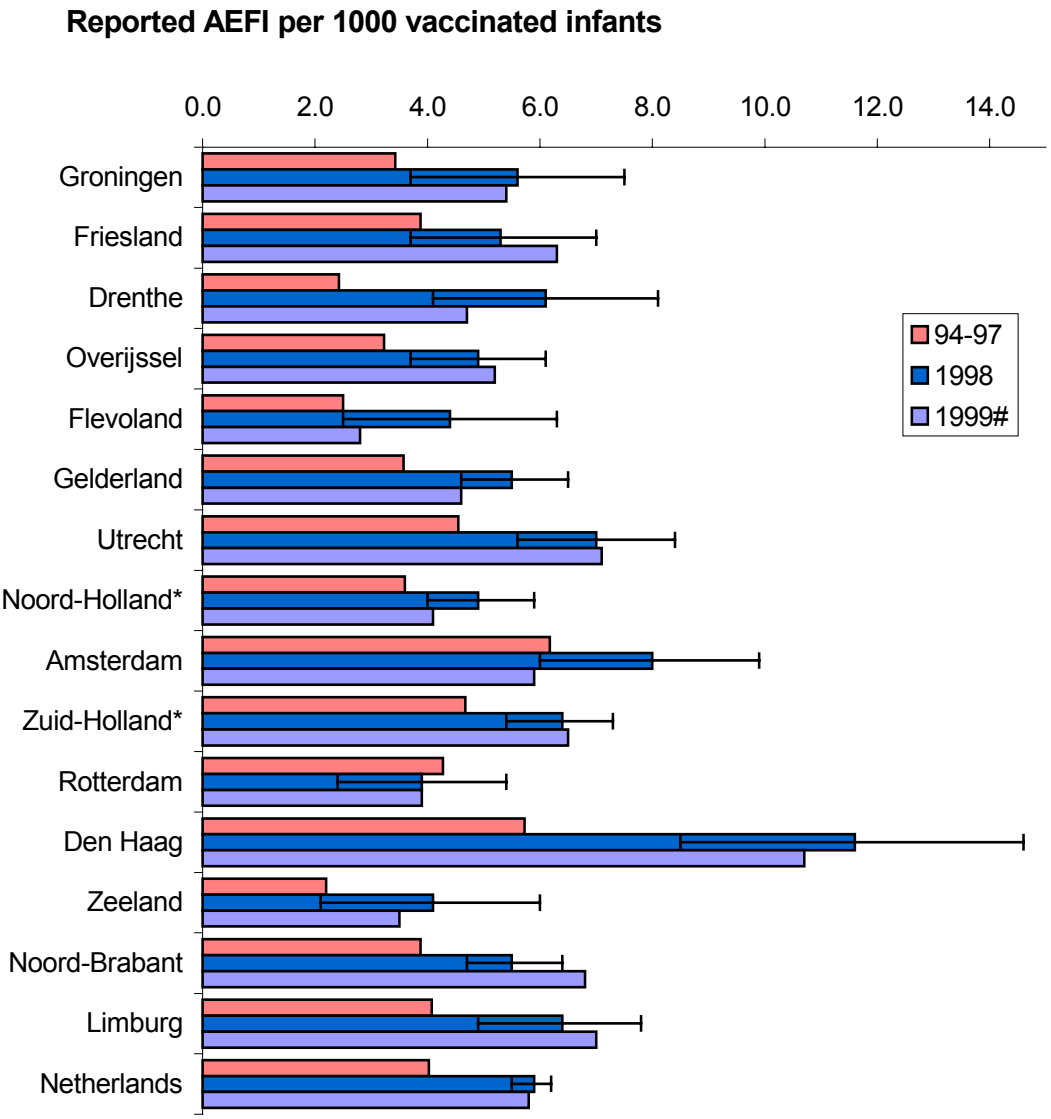
Reports come from all over the country, but are not evenly spread. Standardisation of the rate per 1000 vaccinated infants is increasingly hampered because accurate numbers of the birth cohorts per region and vaccination coverage have not been made available as yet for cohorts

1997 onwards. The birth cohort increased from a little below 190.000 in 1996 to 201.000 in 1999. The distribution of the increase is probably not even over the different regions. Moreover in the year under report approximately extra 17.000 children received the first three DPTP/Hib vaccinations because of the change in schedule to an earlier age.
We have approximated the number of vaccinated infants per region as well as possible. Since there will be inevitable inaccuracies in the presented rates we will not comment upon them into too much detail as yet. As soon as accurate numbers become available the tables will be adjusted accordingly and commented upon as appropriate. See table 4 and figure 1.
Comparing the different regions over 1998 and 1999 does not show very much change.

Table 4. Regional distribution of reported AEFI in 1994-1999, per 1000 vaccinated infants[a]

	1993	1994	1995	1996	95% c.i. [b]	1997	95% c.i. [b]	1998	95% c.i. [b]	1999 [c]	95% c.i. [b]
Groningen	3.2	3.1	4.3	3.5	2.0-4.9	2.8	1.5-4.1	5.6	3.7-7.5	5.4	3.6-7.1
Friesland	1.2	2.5	4.7	3.6	2.2-5.0	4.7	3.1-6.2	5.3	3.7-7.0	6.3	4.6-8.0
Drenthe	1.1	1.8	2.0	3.2	1.7-4.7	2.7	1.3-4.1	6.1	4.1-8.1	4.7	3.0-6.4
Overijssel	1.9	2.1	4.0	2.7	1.8-3.5	4.1	3.0-5.2	4.9	3.7-6.1	5.2	4.0-6.3
Flevoland	0.5	1.4	3.4	2.6	1.2-4.1	2.6	1.2-4.1	4.4	2.5-6.3	2.8	1.3-4.3
Gelderland	1.6	2.9	4.0	3.5	2.7-4.3	3.9	3.1-4.7	5.5	4.6-6.5	4.6	3.8-5.5
Utrecht	3.5	4.6	4.2	4.4	3.3-5.5	5.0	3.8-6.2	7.0	5.6-8.4	7.1	5.7-8.4
Noord-Holland [d]	1.7	2.4	3.8	3.9	3.1-4.7	4.3	3.4-5.2	4.9	4.0-5.9	4.1	3.3-5.0
Amsterdam	4.7	8.2	6.0	4.4	2.9-5.8	6.1	4.4-7.8	8.0	6.0-9.9	5.9	4.6-7.9
Zuid-Holland [d]	3.3	4.6	5.0	4.5	3.7-5.2	4.6	3.8-5.3	6.4	5.4-7.3	6.5	6.0-7.4
Rotterdam	3.6	4.1	5.4	3.1	1.7-4.5	4.5	2.9-6.1	3.9	2.4-5.4	3.9	2.5-5.4
Den Haag	7.0	6.0	3.0	7.3	4.8-9.7	6.6	4.3-9.0	11.6	8.5-14.6	10.7	7.9-13.5
Zeeland	0.5	1.2	2.5	2.2	0.8-3.6	2.9	1.3-4.5	4.1	2.1-6.0	3.5	1.8-5.2
Noord-Brabant	2.4	3.3	3.7	4.3	3.5-5.0	4.2	3.4-4.9	5.5	4.7-6.4	6.8	5.9-7.8
Limburg	1.5	3.4	4.2	3.4	2.3-4.4	5.3	4.0-6.6	6.4	4.9-6.8	7.0	5.6-8.4
Netherlands [e]	2.6	3.6	4.2	3.9	3.6-4.2	4.4	4.1-4.7	5.9	5.5-6.2	5.8	5.5-6.2

[a] for 1997 and 1998 figures of cohort 1996 are used since IGZ has not yet published coverage over 1997 -1999
[b] proportionate confidence interval
[c] for 1999 figures adjusted with approximation of higher number of vaccinated infants because of change in schedule
[d] provinces without the three big cities (Amsterdam, Rotterdam, Den Haag)
[e] the Netherlands have a birth cohort of approximately 200.000 per year and coverage of 97% on average



for 1999 rates are based on birth cohort 1996 with approximation of increase in vaccinated infants because of the change in schedule to an earlier start.
for 1998 the numbers of vaccinated infants per region of 1996 are used because accurate numbers on 1998 are not yet available.

* provinces without big cities Amsterdam, Rotterdam, Den Haag

Figure 1. Number of reported AEFI in 1994 to 1999 per 1000 vaccinated infants

6.4 Vaccines

In 1999 most notifications were about recent vaccinations, all except 30. These latter notifications arose from concerns about planned booster vaccination or vaccination of younger siblings; in over half of these cases parents called. The vaccine involved in these late reports was often MMR (12). Three reports concerned adverse events in previous generation, mainly for vaccination (policy) of new-borns. 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 (394), with declining numbers on subsequent vaccinations and older age, respectively 227, 166, 188 for second, third and fourth dose. For actually simultaneous DPTP/Hib vaccinations numbers increased from 853 to 954, partly reflecting increased numbers of administered doses possibly. For all other vaccines and combinations the numbers are very similar to 1998. In 20 reports DPTP was given singly (22 in 1998), without simultaneous other vaccines. One report concerned single HepB vaccination. Seven children received DTP(olio) instead of the scheduled DPTP by parental choice or perceived contraindications.

Table 5. Schedule and vaccines of reported AEFI in 1999

vaccine given⇒ scheduled ⇓	dptp	dptp hib	hib	dptp hib mmr	dptp mmr	mmr	dtp	dtp hib	dtp mmr	hepb	bcg	flu	other	total 1999	1998	1997	1996	1995	1994
dptp1+hib1	7	384[a]	1	-	-	-	2[b]	-	-	-	-	-	-	394	372	323	284	324	300
dptp2+hib2	3	220	-	-	1[c]	-	2[b]	1[b]	-	-	-	-	-	227	205	142	139	141	126
dptp3+hib3	2	163[d]	-	-	-	-	-	1[b]	-	-	-	-	-	166	148	103	96	103	91
dptp4+hib4	3[e]	180[f]	1	4[g]	-	-	-	-	-	-	-	-	-	188	148	95	88	83	70
dose?	1	6	-	-	-	-	1[b]	-	-	-	-	-	-	8	14	7	4	9	2
mmr1	-	-	-	-	-	139[h]	-	-	-	-	-	-	-	139	139	98	80	95	74
dtp5	4[i]	1[i]	-	2[i]	-	-	27[j]	-	1[i]	-	-	-	-	35	34	22	24	18	11
dtp6+mmr2	-	-	-	-	-	1	1	-	31[k]	-	-	-	-	33	33	25	13	21	21
hib catch-up	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	3	8
other	-	-	-	-	-	-	-	-	-	1	1	-	4[l]	6	7	7	4	3	9
total 1999	20	954	2	6	1	140	33	2	32	1	1	-	5	1197	1100	822	732	800	712

[a] once with hepb vaccine
[b] pertussis left out for non medical reasons
[c] with mmr0
[d] once dptp3/hib2
[d] once first catch up dose
[e] once first and once second catch up dose
[f] once first catch up doses and once dptp4/hib1
[g] once first catch up doses, and once mmr0
[h] twice mmr0 and once mmr2 accelerated schedule
[i] catch up doses
[j] once first dose late starter
[k] once unknown dose numbers
[l] hib and pneumovax, yellow fever, t and opv, t and tig

In 1999 MMR was involved 179 times of which 148 concerned the first MMR (four times before the age of one year) in nine cases with simultaneous other vaccines. Four of these children had their first catch up dose of MMR at a later age. 31 reports were about the regular MMR2 in all but one with simultaneous DTP.
DTP (booster) vaccination at 4 years (approx.) of age was involved 28 times, twice in catch up schedule (once with MMR1); another seven children got DPTP (re) vaccination because

of catch up schedule (once with Hib and once with Hib plus MMR1). Reports concerned (re) vaccination at school age 33 times, of which once only MMR and once only DTP.
The slow decrease in the relative frequency of reported events after the first vaccinations, more or less compensated with reports after the next dose continues. Even more so with regard to the increased number of first (three) doses administration in 1999 when two schedules were applied in the year under report. The number of reports following the fourth dose is still going up however. Compared to 1998 the overall increase in reports is 9%, all on account off reports following simultaneous DPTP/Hib vaccinations for which the increase is 12% (all doses combined). The increase for the first (scheduled) dose is 6% and goes up for dose two and three (11% and 12%) to a 27% increase for dose four. The number of reports following the fourth vaccination is double the number of 1997 and before.
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. For these young-age specific adverse events numbers of reported collapse have gone up but for discoloured legs numbers were stable. It should be noted however that in the year under report two different sub-populations are included: infants following the old schedule and infants following the new schedule. (See also the specific event categories under paragraphs 6.9).
Convulsions, especially febrile, are reported more frequently after the fourth DPTP/Hib and the first MMR, than at younger ages. The relative frequencies of the events over the different vaccines/doses however, are comparable over the listed years (figure 2).
No children with anaphylactic shock were reported and one case of (possible) encephalopathy /encephalitis after MMR1.

Table 6. Event category and (scheduled) vaccine dose of reported AEFI in 1999

vaccine⇒* / event ⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/hib?	mmr1	dtp5	dtp6/mmr2	other	total 1999	1998	1997	1996	1995	1994
local reaction	27	12	13	16	1	2	6	11	1	89	69	49	46	39	31
general illness minor	102	75	58	62	5	55	7	8	1	373	405	254	244	280	242
major	15	15	13	38	-	20	7	1	2	111	85	57	51	55	61
persistent screaming	21	8	4	1	-	-	-	-	-	34	29	26	16	22	37
skin symptoms	19	17	9	13	-	18	5	3	1	85	75	74	58	61	78
discoloured legs	49	44	23	12	1	1	-	-	-	130	125	95	99	93	43
faints	152	44	27	4	-	-	8	9	1	244	174	155	134	147	141
fits	8	11	17	41	1	41	2	1	1	123	133	108	73	97	74
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	-	-	1	-	-	-	1	-	1	2	1	-
death	2	1	2	1	-	1	-	-	-	7	5	3	9	5	5
total	394	227	166	188	8	139	35	33	7	1197	1100	822	732	800	712

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

Of the different event categories the relative increase is largest in the faints category, also in absolute numbers. All reported events are included in the numbers irrespective of causality. See for degree of causality paragraph 6.8, and also the specific events under paragraphs 6.9.
The relative frequency of the different event categories is more or less the same over the years (figure 3). In local reactions there appears to be a steady increase in reports, low still in

absolute numbers however. Minor illness stands out a little in 1998 and is a little above the range of the four previous years, but is again 31% for 1999. For major illness, not necessarily causally related, relative frequency goes up a little and for fits and skin symptoms a little down perhaps. In 1998 the relative frequency for collapse reactions was below the range of 1994-1997, but for 1999 is in the range of 1997 and before again however. Actual numbers have gone up substantially however, compared to 1998.

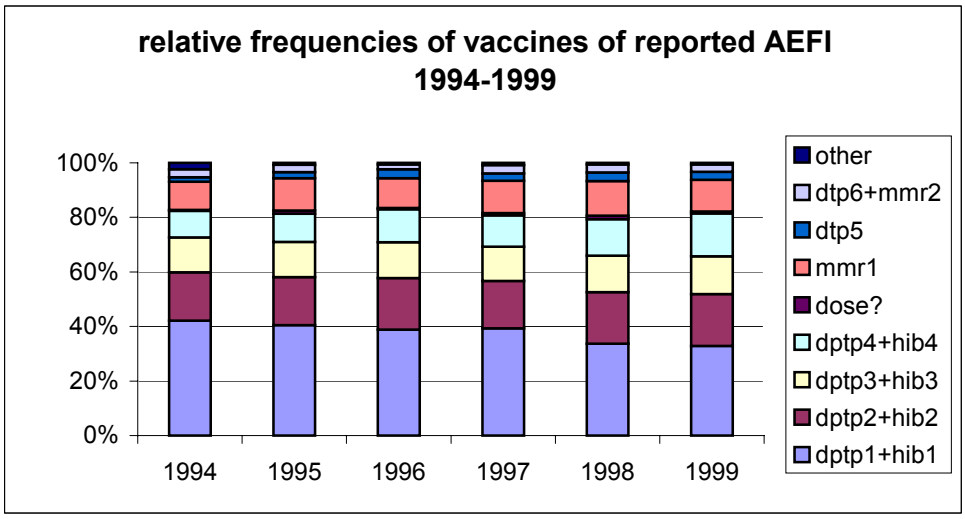


Figure 2. Relative frequencies of vaccine doses in reported AEFI in 1994-1999

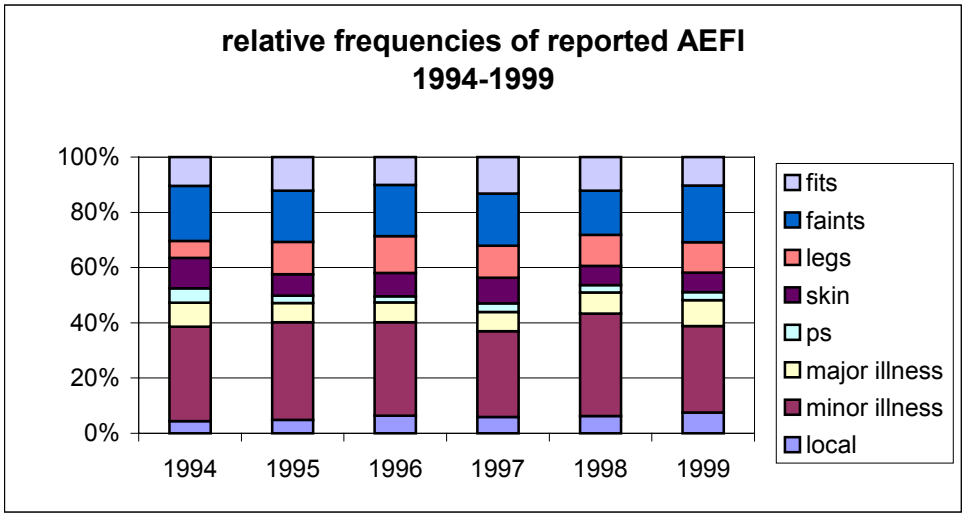


Figure 3. Relative frequencies of events in reported AEFI 1994-1999

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 achieved in the notifying phone call. And in about another 15 percent final assessment did not change the preliminary evaluation substantially. The other 50 percent of reports however could only be assessed after further verification and additional information. In over one third of notifications the original information lacked essential data and in equal percentage 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). In 1999 6% of reports got a full written account .

Table 7. Feedback method and events of reported AEFI in 1996-1999

event ⇓ feedback method⇒		written	tel.	1996 total	written	tel.	1997 total	written	tel.	1998 total	written	tel.	1999 total
local reaction		7	39	46	-	49	49	-	69	69	-	89	89
general illness	minor	21	223	244	3	251	254	4	401	405	5	368	373
	major	16	35	52	16	41	57	14	71	85	21	90	111
persistent screaming		1	15	16	-	26	26	-	29	29	-	34	34
skin symptoms		7	51	58	4	70	74	1	74	75	2	83	85
discoloured legs		14	85	99	4	91	95	1	124	125	9	121	130
faints		36	98	134	20	135	155	9	165	174	18	226	244
fits		29	44	73	25	83	108	14	119	133	11	112	123
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		2	-	1	1	-	1	-	-	-	1	-	1
death		8	1	9	3	-	3	5	-	5	7	-	7
total		141	591	732	76	746	822	48	1052	1100	74	1125	1197

6.6 Source of Information and Medical Intervention

In a little over one third of the notifications the reporter was the sole informant, in 67% information was received from others also, equal to 1998 (table 8). In 92% the clinics (child health care, school health and refugee clinics) supplied information. Parents were in 63% (756) of cases contacted, some times during the notifying telephone call at the Child Health Clinic. This percentage is similar to 1998 and parents were the sole informer of 40 reports (in 1998 21 times). Hospital specialists supplied information in 19% of the reports, more than in 1997 and 1998 (15%), meaning again an increase of 61 in actual numbers.

The increase in numbers is reflected in more parents notifying and in more hospital contact. The level of medical intervention sought or received may also illustrate the impact of adverse events. In 24% (289) of reported events no professional medical help was sought or was not recorded by us and 12% of the parents (143) administered paracetamol suppositories or diazepam by rectiole for instance. Nearly 64% of the parents contacted the clinic or GP, called the ambulance, or went to hospital, with 12 % admittance. In 1997 and 1998 these latter percentages were 52% and 60% and 11% and 10 % for admittance. In table 9 intervention is ordered according to highest level used.

Table 8. Information sources and events of reported AEFI 1999

																Total
info ⇒	clinic*	+	+	+	+	+	+	+	+	-	-	-	-	-	-	1099
	parent	-	+	+	+	+	-	-	-	+	+	-	-	-	-	757
	gen. pract.	-	-	-	+	+	-	+	+	+	-	+	-	-	-	34
	hospital	-	-	+	-	+	+	-	+	-	-	-	+	-	-	229
	other	-	-	-	-	-	-	-	-	-	-	-	-	+	-	3
event ⇓	unknown	-	-	-	-	-	-	-	-	-	-	-	-	-	+	7
local reaction		37	34	3	5	-	2	-	2	1	3	-	2	-	-	89
general illness	minor	136	158	31	6	2	7	4	-	1	16	1	5	-	6	373
	major	31	36	17	6	2	13	1	-	1	4	-	-	-	-	111
persistent screaming		18	15	-	-	-	-	-	-	-	1	-	-	-	-	34
skin symptoms		33	32	3	3	1	3	-	-	-	6	-	2	1	1	85
discoloured legs		24	80	17	2	-	2	-	-	-	2	1	2	-	-	130
faints		31	153	42	5	1	5	1	-	-	5	-	1	-	-	244
fits		14	42	35	2	5	13	1	2	-	4	2	1	2	-	123
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-it is		-	-	-	-	-	1	-	-	-	-	-	-	-	-	1
death		-	-	1	-	1	3	-	2	-	-	-	-	-	-	7
total		324	550	149	29	12	49	7	6	3	41	4	13	3	7	1197

* child health , school health and refugee clinic

Table 9. Medical intervention and events of reported AEFI in 1999

intervention⇒ / event⇓		?	none[a]	supp[b]	clinic[c]	gp tel[d]	gp visit[e]	ambu lance[f]	out-patient	emerg ency	hospital stay	other	post mortem	total
local reaction		10	12	12	18	4	21	-	9	2	1	-	-	89
general illness	minor	85	30	51	34	20	86	-	21	8	25	13	-	373
	major	16	1	17	2	10	27	-	5	-	33	-	-	111
persistent screaming		9	3	12	2	2	5	-	-	1	-	-	-	34
skin symptoms		12	5	3	11	6	32	-	9	2	3	2	-	85
discoloured legs		22	10	30	14	9	25	1	3	6	10	-	-	130
faints		27	33	15	27	31	52	4	14	7	31	3	-	244
fits		10	1	3	1	7	27	13	15	9	37	-	-	123
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		-	-	-	-	-	-	-	-	-	1	-	-	1
death		-	3	-	-	-	-	-	-	-	-	-	4	7
Total 1999		191	98	143	109	89	275	18	76	35	141	18	4	1197

[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

6.7 Sex Distribution

Overall more boys (54%) were reported than girls, similar to 1998 but slowly decreasing in the last four years from the 60% in 1994 en before (table 10). Distribution over the different events ranged from 50% (convulsions) to 56% boys (minor illness) with events with less than

40 reports excluded. See for specifics on the events and subdivision, the respective categories under paragraph 6.9.

Table 10. Events and sex of reported AEFI in 1998 and 1999

event ⇓		sex⇒	male	female	unknown	1998 total	male	female	unknown	1999 total
local reaction			33	31	5	69	44	42	3	89
general illness		minor	209	185	11	405	201	159	13	373
		major	49	36	-	85	58	53	-	111
persistent screaming			19	10	-	29	19	14	1	34
skin symptoms			40	29	6	75	50	34	1	85
discoloured legs			69	55	1	125	70	58	2	130
faints	collapse		80	77	1	158	119	102	-	221
	BHS		2	2	-	4	-	5	-	5
	fainting		6	5	1	12	9	8	1	18
fits	convulsions		34	31		65	37	38	2	77
	epilepsy		1	2	-	3	1	2	-	3
	atypical attacks		37	28	-	65	23	20	-	43
anaphylactic shock			-	-	-	-	-	-	-	-
encephalopathy/-itis			-	-	-	-	-	1	-	1
death			2	3	-	5	6	1	-	7
total			581	494	25	1100	637	537	23	1197

Under unknown are several cluster reports of minor illness, local reactions and some unsubstantiated rumours.

6.8 Causal Relation

Adverse reactions are events with (likelihood of) causality assessed as certain, probable or possible. In 1999 in 84% of reports were considered adverse reactions, somewhat higher than in 1998 and 1997 (80%) and excluding non-classifiable events. The other events were considered coincidental events with improbable or absent causal relation with the vaccinations. 12 Notifications were not classifiable (1%).

Table 11. Causality and events of reported AEFI in 1999

event ⇓		causality⇒	certain	probable	possible	improbable	non classifiable	total	(% AR)*
local reaction			54	25	8	1	1	89	(99)
general illness		minor	-	130	143	95	5	373	(74)
		major	-	35	42	34	-	111	(69)
persistent screaming			-	34	-	-	-	34	(100)
skin symptoms			-	5	49	31	-	85	(64)
discoloured legs			-	115	13	2	-	130	(98)
faints	collapse		-	201	11	8	1	221	(96)
	BHS		-	4	1	-	-	5	(100)
	fainting		-	16	1	1	-	18	(94)
fits	convulsions		-	25	44	6	2	77	(92)
	epilepsy		-	-	-	3	-	3	(0)
	atypical attacks		-	11	26	4	2	43	(90)
anaphylactic shock			-	-	-	-	-	-	-
encephalopathy/-itis			-	-	1	-	-	1	(100)
death			-	-	2	4	1	7	(33)
total			54	601	341	189	12	1197	(84)

* percentage of adverse reactions (causality certain, probable, possible) of total number of reported events.

There are great differences in causality over the different event categories, but over the years very consistent. See for description and more detail the specific paragraphs under 6.9 and discussion in chapter 7. For MMR vaccination 69% of reported adverse events were considered an adverse reaction in 1999. This was higher than in 1998 and 1997 (50% and 53%). For DTP, DPTP and Hib vaccinations this percentage was 85%, a little lower than in 1998 (88%) and higher than in 1997 (80%).

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 1999.

6.9.1 Local reactions

In 1999, 89 predominant local reactions were reported in approximately equal frequencies after DPTP/Hib or DTP vaccinations (table 12). All but two reported local events were considered reactions (table 11).

Mostly (60) they were mild or moderate reactions of common inflammation with in 32 cases atypical symptoms, like some kind of local rash (10), possible infection (2), lymphadenopathy (4), (de-) pigmentation (3), haematoma /fibrosis and dimpling (6), only swelling or itch. 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". Mostly the symptoms were one-sided, in majority DPTP (29) but five times definitely both sided and six times Hib. In 25 reports the site was not specified.

Of the 22 Children with so called major local reactions, nine had extensive common inflammation, one extreme "avoidance behaviour" and one a swollen armpit with in the biopsy fatty tissue and non-specific inflammation. This latter report was not classifiable. Of the eleven abscesses four were drained surgically and seven drained spontaneously. The only culture performed was negative. No faulty procedures were revealed. Once the abscess was accompanied by very high fever of $\geq$40.5°C.

There was an increase in reported local reactions, again as in 1998 mainly following DPTP/Hib vaccinations, both in the numbers of minor reactions as in the number of major reactions.

Table 12. Local reactions and vaccines of reported AEFI in 1999

vaccine⇒ / event⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/hib?	mmr1	dtp5	dtp6/mmr2	bcg	total 1999	1998	1997	1996	1995
mild/moderate	9	2	4	7[b]	1	-	3	2	-	28	32	28	20	16
severe/prolonged	4	1	-	-	-	1	2[c]	3	-	11	6	8	7	6
abcess	4	4	2	1	-	-	-	-	-	11	9	-	4	2
atypical moderate	9[a]	5	5	5	-	1	1	5	1	32	22	13	15	15
avoidance	1	-	2	3	-	-	-	1	-	7	nr	nr	nr	Nr
total	27	12	13	16	1	2	6	11	1	89	69	49	46	39

[a] once dptp only and once hib only
[b] once dptp only and once first catch up dose
[c] once first dptp/hib/mmr catch up dose and once first dose dtp

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. Depending on severity there may be subdivision in minor or major.

minor general illness

In 373 children the complaints were considered minor illness in 1999, in 26% with no causal relation with the vaccination (28% in 1996, 1997 and 1998) (see also table 11). 78% of reports concerned the scheduled DPTP/Hib vaccinations, most frequently events following the first DPTP/Hib with increasing relative share of later doses (83% and 87% and 79% in 1996, 1997 and 1998 respectively) (table 13). For comparison the numbers of 1994-1998 are included.

Table 13. Minor illness and vaccines of reported AEFI in 1994-1999

scheduled vaccine ⇓	1994	1995	1996	1997	1998	1999
dptp/hib1	104	102	85	100	117	102[a]
dptp/hib2	53	54	47	53	81	75[b]
dptp/hib3	37	46	34	42	60	58[c]
dptp/hib4	13	27	32	23	54	62[d]
dptp/hib?	?	3	1	2	6	5[e]
dptp/hib/mmr1	?	2	3	1	-	-
mmr1	20	31	32	22	62	55[f]
dtp5	3	6	9	3	11	7[g]
dtp6/mmr2	5	9	1	7	12	8[h]
other	7	-	-	1	2	1[i]
total	242	280	244	254	405	373

[a] twice dptp only and once dptp/hib/hepb
[b] twice dptp only and once dptp/hib/mmr0
[c] three times dptp only
[d] once dptp only, once hib only and twice dptp/hib/mmr
[e] once dtp unknown dose number
[f] once mmr2 in accelerated schedule
[g] once dptp/hib/mmr in catchup schedule and once only dptp
[h] once mmr only
[i] once t and opv in alternative setting

Only very few times it was possible to make a definite diagnosis, mostly working diagnoses were used. These are listed in table 14. Fever was the most frequent (working) diagnosis, 92, once only sub-febrile temperature (37.5-<38.5°C). In all but nine cases the fever was considered possibly causally related. Fever was also the most frequent symptom in the other diagnoses (140 times). Crying was the second most frequent main symptom (48), 29 times vehemently and 12 times prolonged and seven times increased or unusually pitched; in two cases the crying had other causes. There often was pronounced crying in the other events also (50) or groaning (10). Irritability was quite frequently diagnosed (5), as were chills (10) and (sleeping) jerks or myoclonics (25), with or without fever, as often as main working diagnosis as in accompanying symptoms. Apathy or sleepiness was the main feature in 4 cases. Pallor as main or sole symptom was quite frequent as well (26), as were gastric-intestinal complaint (28). Respiratory tract symptoms like common cold, tonsillitis, pseudocroup, pneumonia, otitis, asthma, bronchitis etceteras, were frequently diagnosed (29). Like other years there

were a few children with bulging fontanel (2), both times possibly causally related. In 1999 two children with red urine (myoglobinuria?) were reported, in one with possible recurrence after subsequent vaccination. Twice red urine was reported in events listed under the other specific categories also. Of the children with (possible) rash illness nearly half (21) were considered to be "vaccinitis" following MMR and of the other 23 all but three were judged to be coincidental events. See for further symptoms and causality table 14.

Table 14. Main (working) diagnosis or symptoms in minor illness of reported AEFI in 1999 (with number of adverse reactions)

symptom or diagnosis	1998	(adverse reaction)	1999	(adverse reaction)	symptom or diagnosis	1998	(adverse reaction)	1999	(adverse reaction)
fever	135	(118)	92	(83)	pallor and/or cyanosis	27	(27)	26	(26)
low temperature	-	-	1	(-)	jaundice.	-	-	1	(-)
crying	50	(47)	48	(46)	liverfunction abnormalities	-	-	1	(-)
groaning	-	-	1	(1)	rash (illness)	25	(2)	23	(3)
irritability	10	(7)	5	(5)	vaccinitis	9	(8)	21	(21)
meningismus	1	(-)	1	(1)	parotitis	3	(2)	3	(2)
myoclonics	16	(15)	25	(22)	swelling face/hands/?	4	(2)	5	(5)
chills	13	(13)	10	(9)	lymphadenopathy	2	(1)	1	(-)
bulging fontanel	2	(-)	2	(2)	infectious disease	3	(-)	3	(-)
listlessness	1	(1)	1	(1)	allergy	1	(-)	3	(-)
drowsiness	3	(2)	3	(3)	feeding difficulty	6	(4)	3	(2)
prolonged sleep	8	(8)	1	(1)	vomiting	3	(2)	4	(4)
behavioural problem/ - illness	5	(-)	10	(7)	diarrhoea	2	(-)	1	(1)
neck pain/stiffness	2	(2)	-	-	gastro-enteritis	11	(4)	18	(7)
arthralgia/arthritis/coxitis	3	(2)	-	-	dehydration	1	(-)	-	-
hypertonia	-	-	1	(1)	obstipation/ belly ache	-	-	2	(-)
lying still/frozen	10	(8)	3	(2)	myoglobinuria?	4	(4)	2	(2)
limping/falling	3	(2)	-	-	urinary tract infection	1	(-)	-	-
apnoea	1	(-)	1	(1)	epistaxis	1	(-)	-	-
low saturation	-	-	1	(1)	hyperventilation	-	-	2	(2)
asthma (attack)	2	(-)	2	(1)	whiplash	1	(1?)	-	-
airway infection	16	(-)	18	(-)	headache/migraine	2	(-)	-	-
cough	2	(-)	3	(-)	rolling eyes	1	(1)	4	(4)
dyspnea/wheezing	1	(-)	5	(4)	retardation	-	-	3	(-)
pseudocroup	1	(-)	2	(-)	(congenital) nystagmus	1	(-)	1	(-)
tonsillitis	1	(-)	1	(-)	transient episode undefinable	4	(1)	2	(2)
otitis	1	(-)	1	(-)	not specified	6	(2)	6	(1)

Of the reported AEFI 67 concerned MMR vaccine with in 40 cases a possible causal relation, of which four times attributed to simultaneous DTP or DPTP/Hib and twice to either of the used vaccines. Thus in 54% of the reports of minor general illness following MMR vaccination the event was considered adverse reaction. For the other vaccine combinations this was the case in 76%.

major general illness

In 1999, 111 reports were classified as major general illness (52, 57 and 85 in 1996, 1997 and 1998) (table 15). The distribution is more even over the scheduled vaccines than in the minor illness group. For causality see table 16. Overall 77 events were considered adverse reactions (69%, equal to 1998). In the 34 AEFI considered to be chance occurrences the time interval

was not plausible and/or other causes were established. 21 Reports concerned MMR1 (once in combination with DTP) with in nine cases assessed causality. For the other vaccines or combinations 68 (75%, equal to 1998) reported events were considered to be possible adverse reactions.
Very high fever of ≥40.5°C was the working diagnosis in 54 cases and three times there was prolonged high fever. In all but one case causality was inferred. In the other events in this category very high fever was present in 21 cases, in two thirds in the one-year-old children. Of these latter cases, ten times the fever was considered not to be caused by the vaccination. In other event categories there was very high fever in another 34 cases, mainly in febrile convulsions.

Table 15 Major illness and vaccines of reported AEFI in 1999

diagnosis⇓ vaccine⇒	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	mmr1	dtp5	dtp6/mmr2	other	total
high fever	6	11	9[b]	27	2	1	-	1[f]	57
crying/irritability	2	2	-	1	-	-	-	-	5
arthritis/osteomyelitis	-	-	-	-	1	-	1	-	2
apnoea/respiratory insufficiency	3	-	-	-	-	-	-	-	3
guillain barre	-	-	-	-	1	1	-	-	2
pneumonia/otitis	-	-	-	1	1	-	-	-	2
rash illness	-	-	-	2	1	-	-	-	3
vaccinitis	-	-	-	-	5	-	-	-	5
sepsis/bacteriaemia/waterhouse-f	-	-	-	2	1	-	-	-	3
meningitis	-	-	1	-	1	-	-	-	2
myoclonics/chills	-	-	1	-	-	1[c]	-	-	2
nephrotic syndrome/pyelonephritis	-	1[a]	-	-	1	-	-	-	2
closed drain hydrocephalus	-	-	1	-	-	-	-	-	1
ITP	-	-	1	1	2	3[d]	-	-	7
acute cerebellar ataxia	-	-	-	1	-	-	-	-	1
dyspnoea/atshma	-	1	-	-	1	-	-	-	2
dehydration	1	-	-	1	1	-	-	-	3
metabolic disease	1	-	-	1	-	-	-	-	2
pervasive disorder	-	-	-	-	1	-	-	-	1
hypoglycaemia	-	-	-	1	-	-	-	-	1
mumps/whooping cough	1	-	-	-	1	-	-	-	2
infection	1	-	-	-	-	1	-	1[e]	3
total	15	15	13	38	20	7	1	2	111

[a] dtp only
[b] once dtp/hib
[c] dptp catchup dose only
[d] once dtp/mmr1
[e] hib catch up dose
[f] hib5/pneumovax

The two children with (increase in) apnoea were extremely preterm and still in hospital when vaccinated. It was concluded that indirectly this could be caused by the (stress of the) vaccinations. In the other also preterm child the respiratory insufficiency was the result of possible (recurring) sepsis.
The two cases of Guillain Barré Syndrome occurred after too long or too short an interval and had other probable causes like enterovirus infection, as was the case in the reported acute cerebellar ataxia.
ITP was reported more often than in previous years. With three reports of ITP following MMR (once in combination with DTP) and four times following DPTP/Hib or DTP vaccinations. In four cases causality could not be ruled out.

One of the two children with metabolic disorders had acute derangement following fever after the fourth vaccination and in the other the complex pathology before and after the vaccination apparent was part of later diagnosed metabolic disease.
The increase in possibly causally related events is mainly in the high fever and/or irritability groups.

Table 16. Major illness and causal relation of reported AEFI in 1999

diagnosis⇓ causality⇒	certain	probable	possible	improbable	unclassifiable	total
high fever	-	29	27	1	-	57
crying/irritability	-	4	1	-	-	5
arthritis/osteomyelitis	-	-	-	2	-	2
apnoea/respiratory insufficiency	-	1	1	1	-	3
guillain barre	-	-	-	2	-	2
pneumonia/otitis	-	-	-	2	-	2
rash illness	-	-	-	3	-	3
vaccinitis	-	-	5	-	-	5
sepsis/bacteriaemia/waterhouse-f	-	-	-	3	-	3
meningitis	-	-	-	2	-	2
myoclonics/chills	-	1	1	-	-	2
nephrotic syndrome/pyelonephritis	-	-	-	2	-	2
closed drain hydrocephalus	-	-	-	1	-	1
ITP	-	-	4	3	-	7
acute cerebellar ataxia	-	-	-	1	-	1
dyspnoea/asthma	-	-	-	2	-	2
dehydration	-	-	2	1	-	3
metabolic disease (derangement)	-	-	1	1	-	2
pervasive disorder	-	-	-	1	-	1
hypoglycaemia	-	-	-	1	-	1
mumps/whooping cough	-	-	-	2	-	2
infection	-	-	-	3	-	3
total	-	35	42	34	-	111

6.9.3 Persistent Screaming

In 1999, 34 children with persistent screaming were reported (in 1994-1998 respectively 37, 22, 16, 26 and 29). One child with possible persistent screaming is not included but only listed under discoloured legs as fierce crying seems to be part of the discoloured legs syndrome. Fever was reported in ten cases, twice ≥40.5°C. The reported persistent screaming seems age/dose dependent, as has been noticed in former years (see table 6). Local symptoms were pronounced in 13 cases, of which four mainly had (presumed) pain at the injection site and/or avoidance of movement of the legs. Some of the children had both sided local reactions. Additional symptoms were restlessness, feeding difficulty, and pallor. Parents were usually desperate and seven contacted the family physician and one went to the emergency department. We did not record the degree of intervention in nine cases, however (table 9). In all cases the event was considered to be causally related (table 11).

6.9.4 General skin manifestations/phenomenon

In 1999 skin symptoms were the main or only feature in 85 reports (58, 74 and 75 in 1996, 1997 and 1998). Discoloured legs are not included but categorised separately. The numbers and the distribution over the different vaccine doses is rather similar to prior years, reported events most frequently following the first two DPTP/Hib vaccinations and the first MMR. See table 17.

Table 17. Skin symptoms and vaccines of reported AEFI in 1999

vaccine⇒ / symptoms⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	mmr1	dtp5	dtp6/mmr2	other	total
angio-oedema	2	2	1	1	2[b]	-	-	-	8
cellulitis/ulcus	1	-	-	-	1	-	-	-	2
exanthema	6	6	2	6	8[b]	1	2	1[c]	32
cyanosis	1	2	-	-	-	-	-	-	3
cutis marmorata	1	1	-	-	-	-	-	-	2
harlequin	-	-	1	-	-	-	-	-	1
urticaria	2[a]	3	4	3	6	4	1	-	23
eczema (increase)	4	2	1	-	-	-	-	-	7
petechiae	1[a]	-	-	1	-	-	-	-	2
fixed-drug-reaction?	-	-	-	1	1	-	-	-	2
diaper rash	1	1[a]	-	-	-	-	-	-	2
insect sting	-	-	-	1	-	-	-	-	1
Total	19	17	9	13	18	5	3	1	85

[a] once dtp only
[b] twice mmr0
[c] once yellow fever vaccine

All except one event were considered minor. The only major skin problem was cellulitis with secondary invasive disease and considered not related to the vaccinations. Exanthema, urticaria and (increased) eczema were the most frequent symptoms, with also some increase in noted vasomotor swelling/angio-oedema and vasoconstriction with cyanosis or cutis marmorata. There were two children with petechial rash on upper body and face. Children with petechiae on the legs only are categorised under discoloured legs.

Table 18. Skin symptoms and causal relation of reported AEFI in 1999

causality⇒ / symptom⇓	certain	probable	possible	improbable	unclassifiable	total
angio-oedema	-	1	4	3	-	8
cellulitis/ulcus	-	-	-	2	-	2
exanthema	-	-	20	12	-	32
cyanosis	-	2	1	-	-	3
cutis marmorata	-	1	1	-	-	2
harlequin	-	-	1	-	-	1
urticaria	-	-	15	8	-	23
eczema (increase)	-	1	4	2	-	7
petechiae	-	-	1	1	-	2
fixed drugreaction?	-	-	2	-	-	2
diaper rash	-	-	-	2	-	2
insect sting	-	-	-	1	-	1
total	-	5	49	31	-	85

18 Cases concerned MMR1 (twice before the age of 12 months) with 15 times (possible) causal relation. The three times MMR was combined with DTP or DPTP the symptoms were considered to be caused by neither vaccine. This resulted in possible causal relation with MMR in 71%, mainly rashes in the second week after the vaccination (without systemic symptoms) or on the day of vaccination when causal relation could not be ruled out. The

other events were not considered causally related with the vaccination, mostly because of inconceivable time interval. For the other vaccines or combinations, possible causal relation was assessed in 39 out of 67 events (58%), with in the remaining events other causes assessed and/or non-plausible time interval.

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 1999 130 reports were received (93, 99, 95 and 125 in 1995, 1996, 1997 and 1998). Of these 17 were blue legs (14 double-sided), 55 red legs (including four times arms and 27 double-sided) and 30 purple legs (25 double-sided). Of the 46 one-sided discoloration 11 concerned the DPTP leg and once probably the Hib leg but in the other 34 cases this could not be decided. In total, 47 children had petechiae, including 28 reports without noted prior discoloration of the legs (39 times both sided). Three times there were also (some) petechiae in the neck or trunk (table 19).
About 30% of the children had also fever of which six ≥40.5°C. Nearly two thirds of the children exhibited fierce crying of whom three for several hours (once possibly persistent screaming, not listed in that category). Injection site reactions, if any were not pronounced, but 24 times severe pain (four times extreme) was noted/presumed, 18 times without other signs of inflammation. Six children had also collapse reaction. These compound reports are grouped under collapse also. Seven children were reported with recurrent discoloured legs after subsequent vaccinations. Reports of discoloured legs were most frequent after the first DPTP/Hib vaccinations and decreasing in number with dose number and age, with in this year near equal numbers reported after the first and the second vaccinations.
Causal relation with the vaccines was inferred in all but two cases. See table 11.

Table 19. Discoloured legs and vaccines of reported AEFI in 1999

vaccine⇒ / symptoms⇓	dptp/hib1	dptp/hib2	dtpt/hib3	dptp/hib4	dptp/hib?	mmr1	(petechiae)	total 1999	1998	1997	1996	1995
blue legs	6	6	5	-	-	-	(1)	17	25	23	18	21
red legs	22	17[a]	6	8	1	1	(11)	55	56	38	41	47
purple legs	14	10	4	2	-	-	(7)	30	30	23	27	19
petechiae only	7	11	8	2	-	-	(28)	28	14	11	13	6
total	49	44	23	12	1	1	47	130	125	95	99	93

[a] once dptp only

In the year under report the accelerated schedule was implemented, but only for part of the vaccinated infants in this year. The possible effect of this change will be commented upon in the discussion. Further details of this specific adverse event will be published in a separate RIVM report (descriptive epidemiology and follow up of discoloured leg syndrome following childhood 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). In 1999 there were 221 collapse cases (120, 145 and 158 in 1996, 1997 and 1998), five times BHS and 18 fainting in older children. The five children with breath-holding-spells turned blue, after stopping to breath in expiration when fierce 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 and numbers diminishing with dose number and age [28]. This year however, there seems to be an increase in the number of collapse after the first vaccination and to a lesser extend also after the second and third vaccination. The effect of the accelerated schedule is complicated since only part of the infants vaccinated in the year under report started the vaccination at two months of age. See for further information under introduction, chapter 1, and discussion, chapter 7.

Table 20. Faints and vaccines of reported AEFI in 1999

vaccine⇒ event⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dtp5	dtp6/mmr2	other	total 1999	1998	1997	1996	1995
collapse	147[a]	43[b]	27	4	-	-	-	221	158	145	120	137
bhs	4	1	-	-	-	-	-	5	4	4	7	2
fainting	-	-	-	-	8[c]	9[d]	1[e]	18	12	6	7	8
total	151	44	27	4	8	9	1	244	174	155	134	147

[a] three times dptp only
[b] once dptp only and once dtp/hib
[c] once dptp catch up dose
[d] once first dtp catch up dose
[e] hepb vaccine

In 1999 there were eight children with recurrent collapse reported. Some of these children had (very) incomplete episodes. This was clearly more than in the years before 1998. In eight children the collapse was considered not related because of the too long time interval and/or other cause. Once the event was non-classifiable when an older sibling with possible collapse seven or eight years before was mentioned without further information retrievable and we could not check for doubles in the appropriate year either. See also tables 10 and 11 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 a definite diagnosis could not be made and convulsion could not be excluded either, are listed here. (See also paragraph 5.5)

Most reported convulsions were febrile, occurring predominantly after the fourth DPTP/Hib and MMR1 vaccinations. The reported non-febrile convulsions are evenly distributed over the different doses; the atypical attacks tended to be most frequent in the first half year of life (table 21). Fits at the younger ages were less frequently accompanied by fever than at the later doses/older ages, more so in case of convulsions than in the atypical attacks. Altogether 22 children had fever of 40.5°C and over, five times in children with atypical attacks and 17

times with convulsions. See table 10 for sex distribution and table 9 for degree of intervention.

Table 21. Fits and vaccines of reported AEFI in 1999

vaccine⇒ / event ⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/ hib?	mmr1	dtp5	dtp6 mmr2	other	total 1999	1998	1997	1996	1995
febrile convulsion simple	-	1	3	20[a]	-	18	-	-	-	42	39	27	24	23
complex	-	-	1	9	-	14	-	-	-	24	17	18	8	18
tonic	-	-	-	-	-	1	-	-	-	1	2	1	3	10
atypical	1	-	-	-	1	-	2[c]	-	-	4	3	6	3	7
non febrile convulsion	-	1	1	-	-	2	-	1	1[d]	6	4	5	4	6
epilepsy	1	1	-	1	-	-	-	-	-	3	3	5	3	3
atypical attack	6[a]	8	12	11[b]	-	6	-	-	-	43	65	45	28	30
total	8	11	17	41	1	41	2	1	1	123	133	108	73	97

[a] once dptp only
[b] once with mmr1 and once dptp only
[c] once dptp and once dptp/hib catchup doses
[d] t and tig

71 of the convulsions were febrile of which 67 possibly due to the fever caused by the vaccination and considered an adverse reaction. Of the febrile convulsions not considered to be causally related there was other cause established and/or an implausible time interval with the vaccination (three following MMR1 and one after DPTP/Hib2). Two reports could not be classified because of missing information, both anonymous. Once it concerned a preliminary report for which it was not possible to check for double later full report and once it was probably a double report from a different source. Of the six non-febrile convulsions two were considered not causally related to the vaccination, one after MMR1 and one after Tetanus vaccine and immunoglobulin administration. See also table 11.
There were three children with epilepsy reported, with the first seizure two or more weeks after the vaccinations. All were considered not caused by the vaccinations.
43 Reports were classified as atypical attacks, in all but six cases with possible causal relation to the vaccination. In this subcategory there were six children with possible chills and six with myoclonics. Eight children turned blue and cyanotic, twice with possible breath holding spell, two children were hypertonic and another seven limp. Once it was possibly extreme tonic neck reflex because of the painful leg and once possible choking/aspiration of food. None of the children fulfilled the case definitions for collapse or convulsion.
In 1999 MMR was involved in 44 reports, in all but two instances as single vaccine. 38 times causality was inferred with MMR and twice the event was attributed to the other simultaneous vaccines. Thus there was imputed causal relation with MMR in 86% (69% and 66% in 1998 and 1997) and for the other vaccines in 85% (87% and 76% in 1998 and 1997) of reported cases.

6.9.8 Encephalopathy/encephalitis

In 1999 there was one case of encephalopathy following MMR1. It concerned a girl who received her MMR1 two weeks postponed because of respiratory tract infection. Eight days later she was found in bed with cyanosis and convulsions. In hospital she had 38.7°C and

respiratory insufficiency and had extension convulsions. After the convulsions had been stopped she was cardiovascularly in stable condition and oxygen could be withheld. She remained comatose with occasional eye opening. On CT and MRI there were no signs of encephalitis. She did not recover. It was concluded to be post-infectious and/or post-anoxic encephalopathy. No virological cultures or tests were performed. This event was judged to be possibly causally related to the MMR vaccine, other causes have not been ruled out however.

6.9.9 Anaphylactic shock

No cases were reported in 1999. In matter of fact, we have never received notification of anaphylactic shock with inferred causality and/or appropriate time interval in the few cases suspected anaphylactic shock was notified, since the surveillance system was installed.

6.9.10 Death

In 1999 seven notifications came in of children who died after a vaccination of the RVP (table 22). There were six boys and one girl. In only three cases autopsy was performed Four times the events were not considered to be caused or aggravated by the vaccinations. Twice it was judged that the vaccinations might have contributed (indirectly) to the death with severe underlying disease. See case histories below. In one case causality was not classifiable because no autopsy was performed. Since there were only minor precipitating symptoms before the child died it was concluded to be clinical SIDS. In epidemiological studies SIDS is not associated with childhood vaccinations, therefore causal relation seems unlikely in this case also. However it was concluded that causal relation could not be ruled out because death occurred 7 days after the MMR vaccination.

Table 22. Death and vaccines of reported AEFI in 1999

child	sex	age	vaccines	time interval		symptoms/diagnosis	causality*	autopsy
				illness	death			
A	male	3 months	dptp/hib1	minor	<14 hours	sids	no	yes
B	male	15 months	mmr1	6 days	7 days	clinical sids	nc	no
C	female	4 months	dptp/hib3	28 hours	42 hours	possibly metabolic disorder	yes?	yes
D	male	13 months	dptp/hib4	4 hours	6 hours	williams syndrome with severe inoperable heart malformation; acute pulmonary oedema	yes?	no
E	male	3 months	dptp/hib2	-	6 days	several non fatal malformations and signs of septicaemia	no	yes
F	male	5 months	dptp/hib3	1 day	33 hours	possibly metabolic disorder	no	no
G	male	2 months	dptp/hib1	6-7 days	8 days	infection?	no	no

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

Child A, a healthy boy of 3.5 months old was the day of his first DPTP/Hib vaccinations somewhat tearful and restless with sub-febrile temperature and some local reactions. There were no unexpected symptoms. The same night he was found dead in prone position. None of the findings of the extensive post mortal examination could explain death. The SIDS working

party concluded SIDS with several of the acknowledged risk factors present. Epidemiological studies have found no link of childhood vaccinations with SIDS.
Child B was nearly 16 months old when he received his first MMR vaccination. This vaccination had been postponed twice because of sub-febrile temperature. One week after the vaccination he died unexpectedly. Since the day before he ate less and had symptoms of common cold and diarrhoea. The night was uneventful and he was somewhat listless the next day. He may have felt warm but the temperature was not measured. After he had been put to bed in the afternoon he was found dead one hour later. Clinical assessment and microbiological tests could not explain death. Autopsy was not performed.
Child C was a girl of 4.5 months old who died 42 hours following the third DPTP/Hib vaccination. She received paracetamol prophylaxis because of the complaints after the second vaccinations, with one dose before and two doses after the vaccinations. There were no remarkable symptoms on the day of vaccination except for some local reaction. The next day, approximately 28 hours after the vaccination, she vomited and developed swollen legs with fever. She cried high-pitched intermittendly and was less responsive with periods of hypertonicity. She was given paracetamol twice. That night she was breastfed once and put to bed again, with the mother sleeping in de baby's room. Early the following morning the baby was comatose with a peculiar breathing pattern. In hospital she deteriorated and reanimation was unsuccessful. Autopsy revealed no abnormalities except for the already known VSD. The metabolic screening, of a post-mortal sample however showed some abnormalities consistent with metabolic disorder. But a definite diagnosis could not be made. On retrospect there was a remarkable similarity of the complaints after the second and third vaccinations with symptoms starting mainly after 24 hours. It was concluded that in this case there could be derangement of metabolic disorder because of the fever and/or paracetamol. Therefore there could be a possible (indirect) causal relation with the vaccinations.
A younger sibling was later diagnosed with a severe metabolic disorder without a definite diagnosis as yet.
Child D, was a boy with an inoperable congenital heart malformation. His first three DPTP/Hib vaccinations, a little later than the regular schedule with prophylactic paracetamol, were uneventful. The fourth vaccinations were administered at the age of 13 months, with low dosage paracetamol administered at home. Four hours later he was a little fretful and somewhat warm. He slept for some time in the stroller and vomited a little. About half an hour later his respiration suddenly became rattling and frothy pink fluid came through his mouth and nose. He stopped to breathe and when he arrived in hospital was proclaimed dead. Autopsy was not performed. The most likely cause of death was circulatory failure with acute pulmonary oedema. It is possible that the stress of pain and fever, not very pronounced however, have contributed to the (time of) death of this child.
Child E was a boy of 3 months old when he received his second DPTP/Hib vaccinations. There were no adverse events until he was found dead six days later. Autopsy revealed several pre-known or suspected congenital malformations as well as some undetected malformations. There were also signs of septicaemia. This was concluded to be the probable cause of death, with no contribution of the vaccinations.

Child F. A boy of 5.5 months old received his third DPTP/Hib vaccinations, with on the day of vaccination no complaints. The following day he cried a lot and refused to eat and approximately 26 hours after the vaccinations he developed fever, started to vomit and to have diarrhoea with cough. The GP advised extra fluid intake. An hour after his regular bottle he was found unresponsive and cold. Resuscitation was unsuccessful. The parents allowed no autopsy but some of the performed metabolic screening tests were suggestive for metabolic liver disease. Previous hospital admission for respiratory tract infection at the age of four months showed liver steatosis and extreme weight gain. Parents are consanguineous and the family history is positive for severe liver disease. A definite cause of death could not be determined but it is considered unlikely that the vaccinations played a role.
Child G, was a boy of 2 months of age who received his first vaccinations one week postponed because of respiratory infection. He was not ill but still a little wheezing. He developed some fever on the day of vaccination for which paracetamol was given once. Later in the week he drank a little less and had greenish stools. A week after the vaccination he behaved ill without fever but with groaning respiration. That night the baby was restless, did not want to drink and screamed when diaper changed. When he was taken out of his bed at five in the morning he gasped and became lifeless. When the ambulance arrived he was dead. Autopsy was not performed and additional non-invasive examination was not permitted either. A cause of death has not been established but the older brother had at that moment parainfuenza virus pneumonia with possible secondary bacterial infection.
The interval with the vaccinations is considered too long for causal relation.

7. Discussion

Safety of the RVP is guarded by an enhanced passive surveillance system. The exact number of vaccinations is known, because of the registration by the PEA of all vaccines administered on individual level [29,32]. The RVP is embedded in regular Child Health Care with near total coverage, so the programme is delivered by a relatively small group of specifically trained professionals. This is also advantageous for safety surveillance. The existence of a (24 h) central telephone information service for professionals is a most important tool in acquiring notifications and makes very efficient use of resources both on the reporters' end as on the receiving end. The location of this safety surveillance system at RIVM with its available expertise should guarantee that the surveillance is of high quality.
But the Achilles' heel of passive surveillance is underreporting. Especially selective underreporting is of crucial importance. Whether or not the here presented data on reported AEFI are representative will be discussed.
The year under report was followed with special attention, because of the change in schedule from 3, 4, 5 to 2, 3, 4 months of age for all children born in 1999 (and later) [30]. Direct comparison to prior years is not possible because not all children vaccinated in 1999 were subject to the same schedule. The effects of the accelerated schedule will be described when we have studied a full birth cohort.
Because the exact number of vaccinated children ("denominators") for the birth cohorts of 1997 and later have not yet been published comparisons between the different years are increasingly hampered.

7.1 Increase in Number of Reports

There was again an increase in notifications compared to 1998. This is due only to an increase of reported adverse events following the simultaneous DPTP/Hib vaccinations. For the other vaccines of the RVP the numbers are similar to 1998. This could be caused by the increased numbers of children vaccinated partly because of the larger birth cohort but mainly because an extra month-cohort vaccinated with first, second and third dose DPTP/Hib due to the change in schedule. Analysis is hampered however because the Inspectorate of Healthcare has not yet made accurate numbers of the PEA available. See for discussion on doses and schedule under paragraph 7.1.1.
Over the years there seems to be a step up in 1994, which could be explained by the introduction of a new vaccine (Hib) and diminished underreporting, as result of our efforts to achieve this [22,23,24]. There was levelling off of the steady increase in 1996 and 1997. In 1998 increased awareness and possibly increased reactogenicity caused another step-up [25].
Reporting criteria have not changed over the years, but awareness of the professionals and of the public has increased lately, not only by the publicity around the newly introduced vaccines. Recently the need for vaccinations and their safety has been questioned in certain groups in the population. Also public awareness of the severity of the target diseases has diminished now that the illnesses are effectively prevented by the vaccinations [36,37]. This

situation increases the relative importance of potential side effects. This may influence the willingness to report possible adverse reactions as well.

7.1.1 Vaccine Doses and Schedule

The distribution (relative frequency) of reported AEFI over the different (doses of) vaccines and over the different event categories is rather similar to 1994-1998 (tables 5 and 6 and figures 2 and 3). An increase in absolute number of reports is to be expected since a larger number of infants were vaccinated in 1999. Because of the change in schedule it is an estimated extra 7-8% of vaccinees. The increase in reports after the first three doses seems to be in line with this. The increase is larger for dose four than for the first three doses however. For the fourth dose no influence is to be expected from the new schedule. The increase in number of reports has been apparent from 1994 onwards. As has been discussed before (annual reports 1994-1998) this seems to be partly due to decreased underreporting, increased awareness and for the step-up in 1998 also possibly some increase in occurrence of true side-effects [25]. The increase in numbers in 1999 for the fourth dose of DPTP/Hib could well be the result of a change in reporting attitudes with more spontaneous follow up of reported children. Some of the increase in the number of multiple reports may well reflect this phenomenon (44 versus 26 in 1998 and 12/14 in 1996/1997). There seems to be also a tendency to postpone reporting of non-severe and non-contraindicating events until subsequent vaccinations have been administered and information about adverse events is collected. In cases the diagnosis is minor general illness, minor skin or local reactions the notification is regarded as just one report and listed according to the most pronounced/severe event of linked to the latest vaccination (see methods under paragraph 4.2). This might also partly explain the tendency toward further (relative) increase in numbers of reports after the later doses DPTP/Hib.

7.1.2 Events, Severity and Causality

The increase of reported AEFI is not evenly distributed over the different event categories. Some increase/decrease may be random fluctuation. But it could also be that the change of schedule directly or indirectly influenced type and severity of reported events. Since in the year under report two different schedules applied we will have to wait until at least a full cohort has been vaccinated according to the new accelerated schedule.

The increase in number of reported collapse reactions is most pronounced and warrants further investigation however. See under paragraph 7.2.1.

The percentage of adverse reactions (with causality assessed as certain, probable or possible) fluctuates over the years (78-84%). The share of major events, by our definition, with minor events with hospital admission added, increased from 56% and 54% in 1997 and 1998 to 59% in 1999. The rise is only very small however and criteria for hospitalisation do not reflect severity per se and are subject to a lot of vaccine-unrelated factors. The relative frequency of major events regardless of hospitalisation in 1999 is comparable to 1997, but higher than 1998. The higher share of major adverse reactions in 1999 reflects the increase in collapse reactions, which are major events by definition.

7.1.3 Reporters and Reporting Interval

The vast majority of notification is from Child Health Clinic staff, with the proportion of reports from parents increasing (7.6%). The reporting route also is very consistent over the years with nearly all reporting by telephone.
Increased (perceived) severity of events and/or apprehension could lead to shorter reporting interval. In 1999 the reporting intervals were similar to 1998 with for DPTP/Hib 30% of events reported within 4 weeks and 40% notifications around the time of the next clinic visit (30% and 44% in 1998). This seems to point to increased concern if not to increased severity. For MMR1 the reporting interval decreased with 40% of reports within 4 weeks (34% in 1998). This could be the result of increased or awareness in general for adverse events, but possibly also some increased attention since MMR of a different form and presentation from another manufacturer has been distributed in 1999 (and 2000). This was because of a temporary supply shortage of the regular product.

7.1.4 Source of Information and Intervention

Information about the adverse event was retrieved from others than the initial reporter in 67% (66% in 1998). More parents were contacted then the year before, not so much because of the severity of events as well as because of apprehension in parents and providers. Increasingly also the reports have insufficient information, necessary for categorising and causality assessment. Anti-vaccine-movements in the Netherlands add substantially to public concern about possible adverse events. More parents contacted the clinic or phoned the GP than in previous years (198 versus 94 and 168 in 1997 and 1998), an increase in relative frequency to 17% (11% and 15% in 1997 and 1998). The proportion of children actually seen by the GP or in hospital rose to 46% from ~42% in 1997 and 1998.
This also seems to point to increased concern if not to increased severity.

7.1.5 Regional Distribution of Reporting Rates

We have standardised the number of reports per region on rate to vaccinated infants (for the first three doses). Since the actual numbers of vaccination coverage and population in the different regions are not yet made available we will not comment upon the preliminary reporting rates per region.

7.2 Specific Events

7.2.1 Collapse and Discoloured Legs

Reports on collapse reactions seemed to have been rather stable over the last five years, as well as the distribution over the different vaccine doses. In 1999 however there is a significant increase in the reported number and a different distribution over the respective vaccine doses. Since no exact information is available on vaccinated on actual number of vaccinees per dose and the year under report covers only 10 months of the full birth cohort to which the new schedule applies there are to many uncertainties. We think it unwise to speculate on trends and explanations as yet. For discoloured legs the numbers are similar to 1998 but there also has been a change in distribution over the different vaccine doses. The number of compound reports with collapse reaction and discoloured legs is stable over the

years (6, 6, 7 and 8 in 1996, 1997, 1998 and 1999). Since in 1999 children are vaccinated according to two different schedules we will evaluate collapse reactions and discoloured legs once full birth cohorts can be compared.

7.2.2 Convulsions and Atypical Attacks

The number of (classic) febrile convulsions following DPTP/Hib vaccinations is similar to 1998. Since these events are most frequent after the fourth dose and this dose is not affected by the change in schedule, this is not surprising. The number of reports with atypical attacks is lower than in 1998 and comparable to 1997. One has to bear in mind that this is a subcategory for non-specific paroxysmal events that do not fulfil the criteria for collapse or convulsion. So the number is subject to completeness of information also. In the different years there might thus be a not constant transfer to and from other event categories. The stable number of reports of non-febrile convulsions may reflect the non-causality in the first place.

We will take into account also atypical attacks when assessing the effect of the accelerated schedule on reported adverse events in the next annual report.

7.2.3 Local Reactions and Abscess

There seems to be some increase in local reactions especially in atypical presentations and this year toward earlier vaccine doses. Also there were again more reported abscesses. As in previous years no faulty procedures were detected. We will look into risk factors, like eczema and possibly parents working in health care also to decide on risk factors for abscess formation in the coming years.

7.3.3 Death

This year seven children who died were reported. This is according to expectations, regarding the average over the years. Systematic studies and evaluation of the Institute of Medicine have shown infant death not to be related to childhood vaccinations [37,38,39]. In an individual case however this may not be easily demonstrated. Especially in the case of possible SIDS this might pose a problem. 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 there is an adverse effect on compliance to the programme, of public and professionals, in the direct surroundings of the case.

In the year under report twice the vaccination might have had an (indirect) adverse role in the death of the infant.

The first child had (on retrospect atypical) symptoms after the second vaccination with full recovery. After the third vaccination this recurred but the child deteriorated in the early morning two days after he vaccination and resuscitation was unsuccessful. Post-mortem screening pointed to possible metabolic disorder, for which a younger sibling proved positive. The exact pathophysiological mechanism remains unclear as yet however. It could be that the fever or paracetamol have contributed. There has not clearly been a delay in medical help because inadvertent assumption that the event was a common or well-known transient vaccine reaction. The younger sibling of this child has received vaccinations in hospital

setting with severe derangement after the second doses. This case will be included in the report on 2000.
The second child was a boy with Williams syndrome, accompanied with a severe and inoperable malformation of the heart. The first three doses of DPTP/Hib were well tolerated, and the child fared as well as might have been expected. The fourth dose given at 13 month of age had only some common minor adverse symptoms. Six hours later he produced frothy pink sputum, gasped and passed away. It is felt that the stress of pain and possibly some fever could have contributed and may have compromised the haemodynamics. It is conceivable that the child would not have died that same afternoon had it not been vaccinated. The parents however were eager to have the child protected and there were no valid medical reasons not to vaccinate.
In both cases there might have been (indirect) causality with the vaccination.

7.3 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. Just signal detection isn't enough anymore [38]. (See also under paragraph 7.4) Evaluation and feedback communication should complement mere registration. 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 unavoidable however. Sometimes postponement of vaccination might free the vaccine and vaccination programme of allegations of causing an event or disorder that will inevitably occur. But deferral or postponement should be avoided as much as possible because it will delay protection of the child.

7.3.1 Prevention of Side Effects

Side effects do occur and parents should know what to expect. Also they instruction about what (not) to do to alleviate symptoms. In the communication of 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. Some education of the professionals in this respect seems warranted also. The vaccination as cause should be in the differential diagnosis, nothing more but also nothing less. Proper procedures and techniques are important in minimising adverse reactions and the proper use of paracetamol should be included in the information to parents.

7.3.2 Contraindications

Contraindications for the RVP vaccines have been abandoned more or less completely [27,28,30,39,40]. Proper application of true contraindications should be adhered to however to prevent undue side effects. But false contraindications should be avoided 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 increased 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.

7.3.3 Risk Communication

Increasingly in our telephone information service and in our adverse event surveillance system we are (made) aware of the need (of at least a group of) parents of more balanced and readily accessible information about the pro's and con's of the vaccination programme. But also increasingly providers signal the need of more apt and specific information to communicate to the parents, however better informed as they are over the past years, and for their own "weigh and consider". They need up to date facts and figures. Not only providers but also parents should be systematically informed about the risk-benefit balance of the programme. The successful control of the target diseases causes diminished awareness of the severity of the target diseases and the perceived risk of complications and sequelae. Child Health Care personnel should be equipped for more direct and adequate information and need up to date information on matters. Especially now with the anti-vaccine-movements contributing to much confusion.

7.3.4 Causality Assessment

Causality assessment is of importance both for surveillance purposes of the vaccines and the vaccination programme as well as for individual assessment [41,42]. A lot depends on this assessment regarding the individual continuation of the schedule. For the population served this is of additional importance also, since disquiet is known to result in diminished coverage. Both acknowledging true adverse reactions as well as recognising evidently coincidental events are in this respect of importance. Careful causality assessment may free the programme from the burden of severe but unrelated adverse events as well as detect new rare adverse reactions. It may detect also new as yet unrecognised more common side effects.

7.4 Safety Surveillance of the RVP

Safety surveillance of the vaccination programme seems to be of increasing importance [7,8,43]. The surveillance system will need to be supplemented by more active monitoring and systematic studies. Passive surveillance will however remain the backbone. For purposes of follow up and other forms of systematic study homogeneous event categories with application of case definitions are the core.

Assessing causal relation is regarded essential in monitoring the safety of the vaccination programme [41,42]. Not everything happening after vaccination is caused by the vaccination of course. Only one percent of the reports did not allow causality assessment, mostly by lack of information about time interval or symptoms. All unclassifiable events were considered non-severe or were unsubstantiated rumour, except for one of the children who died (in this case causality was judged to be unlikely also however). Overall 84% of reports were considered adverse reaction, somewhat higher than in 1997 and 1998 but within the range of 1994-1998. Comparison of RIVM with GR assessment shows a remarkable consistency. Safety surveillance with causality assessment by RIVM and GR makes liberal reporting criteria possible and therefore more sensitive signal detecting. Since also adverse events without

presumed causal relation are included in the system signal detection irrespective of time period covered is included. For causal relation five different categories are used, for the purpose of international comparison. International comparison is hampered however because of different criteria for surveillance systems, diagnostic procedures and causality assessment, apart from the use of different schedules and/or vaccines and inconsistent case definitions.

7.4.1 Route of Reporting and Feedback

We feel 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 as with regard to the quality of data. We feel that this low threshold reporting channel has much advantage over written report forms not only because the possibility of communication, timeliness and supplementation of data. It is also an important tool to adherence to the programme, to proper use of contraindications and to adequate vaccination in special circumstances.
It makes very efficient use of resources, may be deceivingly not so apparent at the level of RIVM but in the broader perspective of the management of the vaccination programme as a whole. Education of potential reporters is essential, of course, but for the type of reports in a passive surveillance system this will not yield too much gain in efficiency. One has to bear in mind that adverse events reported in passive surveillance systems are in majority severe rare events and uncommon peculiar or unexpected events or 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 any specific event, age and vaccine and keep up with all medical literature in this respect. Education however, to stress the importance of reporting and about the type of basic information necessary to keep at hand, when reporting may increase efficiency further.
There seems to be an increasing need for the public also to have access to this kind of information service. Also more readily available and accessible general and specific information in print is needed, both for the professionals and the public.

7.4.2 Verification and Assessment

In the monitoring of the safety of the vaccination programme verification and additional information with follow up is considered of utmost importance. A substantial part of supplementation and verification is done in the reporting telephone call. With the written notifications this will have to wait until later.
Categorisation is done using the diagnostic criteria for case definitions and for causality. For the aggregated analysis all cases have been reappraised. Discrepancy is often large between reported diagnosis and final diagnosis. This discrepancy is partly due to different case definitions, but also because of more detailed information and more specific knowledge, skills and experience of the physicians of LVO. 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 [44]. 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 50 years! And for paediatricians also it is a rather rare entity. One tends to mould symptoms in known diagnostic categories. But on the other hand, reported collapse reaction is not always collapse. Often there is only pallor or only apathy or just drowsiness or excessive sleep/difficulty in awakening and symptoms do not meet the criteria for the case definition.
Skin symptoms tend to cause great concern because of the 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 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 very low rate of recurrence after further pertussis vaccinations [27].

7.4.3 Active versus Passive 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 expectations of a change in this respect. A planned study for the tolerability of DPTP/Hib got thwarted because a planned MenB trial was postponed and in between an accelerated schedule for the DPTP/Hib vaccines was adopted. This accelerated schedule however in itself deserves specific study of overall tolerability at a younger age. In 2002/2003 we plan to perform an active study in about 10.000 children for the four doses of DPTP/Hib and MMR1 as part of an EU project, for rare and severe events (EUsafevac). This study may also assess the performance of our current enhanced passive surveillance system. We will try to include a subgroup for the more common minor events to assess tolerability. Also data linkage possibilities will be explored for future use within this EUsafevac project. 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 monitoring through follow up or data linkage designs need to be employed. With relying on only active surveillance (apart from inaccurate data) the safety-surveillance-system is "unmanned" for testing generated hypotheses since that will not be possible anymore. Therefore enhanced passive surveillance as well as hypotheses testing designs are of importance and should be employed in the right order.

7.5 Future Considerations

Consolidation of the current good reporting practices of clinic staff, with continuous education, also of GP's and paediatricians, is an important aspect of good performing vaccination programme. In the Netherlands the low threshold (24h-) telephone service for reporting, consultation and advice is of great value for the current adverse event enhanced-

passive-surveillance system. The quality of data generated by this system allows systematic follow up and study of specific adverse events. Subsequently adjustment of contra-indications and precautions may follow. Detailed trend analysis of specific adverse events, schedules and vaccines or lots will only be possible if a robust database system is available.
Active surveillance to check on overall tolerability may be gained as part of an EU project (EUsafevac). Further more 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. Hypothesis testing however cannot ever be performed within the same system as the system the which the hypothesis was generated.
The newly introduced acellular pertussis vaccine as booster in the four year old (from birth cohort 1998 onwards) will be followed up actively and this study may serve as a pilot for the EUsafevac project. Hospital admission after any vaccine, gait disturbances and ITP after MMR1 are the proposed outcomes to be studied in (prospected) active design. These studies may shed light on ITP and gait disturbances as adverse events and on the relative performance of the current passive surveillance system.
A well performing, good quality safety monitoring system such as exists in the Netherlands cannot be taken for granted but requires maintenance and investment. New epidemiological designs and techniques may expand the knowledge on adverse events but an adequate database system is a prerequisite for this. But also the data put into the system must be of good quality of course. With the 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 combating unfounded allegations. But it is clear also that providers must be supplied with timely referenced information about any suggested association of severe adverse events and vaccination in the media or medical press. Only then it is possible to answer questions from the public. Clinic staff stress that it is much more time consuming to convince parents of the benefits of the vaccination programme than before and that resources fail. Often parents have already a lot of information from other sources and it is not easy if at all possible for them to decide on the quality of the information. 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. Also there is need for fact sheets per target disease and vaccine. Periodic actualisation of the RVP guideline book is also necessary but will not meet the need for timely information to refute unfounded allegations. Lately the Minister of Health has recognised this need in a letter to the parliament about the RVP (2nd of October 2000).

8. Conclusions and Recommendations

In 1999 the increase in number of reported adverse events appears to be mainly due to the increased number of vaccinated infants and possibly also to subsequent uncertainties in providers and parents. Whether there has been an increase in (acknowledged) age specific events and/or a shift across the different doses remains to be seen. This has to be evaluated once the accurate numbers of vaccinees have been made available and once a full birth cohort following the accelerated schedule can be assessed. Periodically the overall tolerability of vaccines of the vaccination programme should be studied with attention to perceptions of providers and parents. The change in schedule from 1999 onwards to an earlier start of the programme makes direct comparison with prior studies not completely possible anymore however. The EUsafevac project study may supply some of the information.
Overall the regional distribution seems satisfactorily, although for some adverse events there seems to be substantial underreporting. We plan to include ITP and gait disturbances following MMR vaccination in one of our data linkage pilots, if possible (EUsafevac).
Detailed study of epidemiology, sequelae, follow up and risk factors should be performed regarding some specific adverse events, e.g. collapse, discoloured legs and atypical attacks/non-febrile convulsions in the near future. Also we will look into the abscess cases for risk factors.
The (24h-) 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. Quality should be maintained and if possible 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 of the future should be prepared to be ready to study signals of specific rare or long-term adverse effects on short notice. Especially now the introduction in the RVP of more (novel) vaccines is foreseen in the forthcoming years. This information may be necessary to counteract allegations of anti-vaccine movements. A problem is that one does not know what the next signal will be. International collaboration should be expanded, towards a comprehensive safety surveillance network of the childhood vaccination programmes. This may also be of help to perform the specific studies and increase scientific knowledge about adverse events following vaccinations. Eventually this will all boost public confidence in the programmes.
For the coming year is planned:

- implementation of a robust database system
- accelerated annual report of 2000 and 2001
- maintenance and evaluation of the current passive surveillance system
- report on descriptive epidemiology of discoloured legs and follow up
- belated report on descriptive epidemiology of collapse reactions and follow up
- exploration and study of possibilities of data linkage or sentinel studies

- design of active study of tolerability of DPTP/Hib vaccinations also in relation to the accelerated schedule with start of the programme at a younger age.
- active follow up of the new acellular pertussis booster vaccine of the four year old children

We plan to keep up a thorough high quality safety-surveillance-system and to stimulate reporting in the coming year. Only then it can be shown that the vaccination programme is safe. The total of 1197 reports must be regarded in relation to a total of nearly 2.5 million vaccines administered with over 6 million components.

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Appendix 1 Mailing list

1	Hoofdinspecteur Preventieve en Curatieve Gezondheidszorg
2	Directeur-Generaal Volksgezondheid
3	Inspectie Gezondheidszorg, Inspecteur Infectieziekten
4	Gezondheidsraad, Den Haag voorzitter
5	Gezondheidsraad, Den Haag secretaris werkgroep RVP
6-22	Safety Surveillance Systems (diverse buitenlandse instellingen)
23	Depot Nederlandse Publikaties en Nederlandse Bibliografie
24	Directie RIVM
25	Directeur sector Vaccins
26	Directeur sector Volksgezondheidsonderzoek
27-29	Hoofd LVO
30-31	Hoofd LCB
32-33	Hoofd LPO
34-35	Hoofd LVR
36-37	Hoofd KRZ
38	Hoofd CIE
39	Hoofd LIS
40	Hoofd LIO
41	Directie SVM
42	Apotheker SVM
43	College ter Beoordeling van Geneesmiddelen
44	LAREB
45-62	Medisch Adviseurs Entadministraties
63	Landelijke Vereninging Entadministraties
64	Landelijk Coördinatiestructuur Infectieziektenbestrijding
65	Landelijk Coördinatiecentrum Reizigersadvisering
66-70	Auteurs
96	SBD/Voorlichting en Public Relations
97	Bureau Rapportenregistratie
98	Bibliotheek RIVM
99-109	Bureau Rapportenbeheer
110-140	Reserve

Appendix 2 Vaccination Programme 1999

4.7 Alle nadere inlichtingen welke niet betrekking tot het vaccinatieprogramma 1999 worden gevraagd, vereisen de goedkeuring van de Hoofdinspecteur voor de Gezondheidszorg.

4.8 Exemplaren van deze folder kunnen worden aangevraagd bij de Inspectie voor de Gezondheidszorg, Parnassusplein 5, Postbus 16119, 2500 BC Den Haag, telefoon (070) 340 5979

4.9 Voor vaccinaties, gegeven overeenkomstig bovengenoemd vaccinatieprogramma, doch zonder tussenkomst van de Provinciale Entadministratiss, worden GPPM gratis vaccins ter beschikking gesteld, mits range vergoeding gegeven.

5 **BIJWERKINGEN**

Na vaccinaties kunnen in zeldzame gevallen (ernstige) bijwerkingen optreden.
Elke bijwerking kan de vaccinatiegraad negatief beïnvloeden.
Melding van (mogelijke) bijwerkingen aan het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) te Bilthoven, onder vermelding van het partijnummer van het betreffende vaccin, is dan ook dringend gewenst (tel. (030) 274 24 24, fax (030) 274 44 30)

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 maanden	DKTP 4 + Hib 4
14 maanden	BMR-1
4 jaar	DTP 5
9 jaar	DTP-6 + BMR-2

Den Haag, december 1998

De Hoofdinspecteur voor de Gezondheidszorg

J. Verhagen

STAATSTOEZICHT OP DE VOLKSGEZONDHEID

Inspectie voor de Gezondheidszorg

VACCINATIEPROGRAMMA 1999

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

1999	1998	1995	1990
DKTP + Hib	DKTP + Hib + BMR	DTP	DTP + BMR

LET OP
In 1999 zijn belangrijke wijzigingen in het vaccinatieschema aangebracht.

1. **ZUIGELINGEN en KLEUTERS**

Vaccinatieschema

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

Op de leeftijd van respectievelijk **2, 3** en **4 maanden** wordt **één** DKTP-injectie gegeven.
De minimum leeftijd voor de eerste injectie is 7 weken. Het dient minimaal een periode van **4 weken** in acht te worden genomen tussen de drie vaccinaties.
De vierde DKTP-injectie 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-injectie en de vierde DKTP-injectie.
Dosering: 1 ml INTRAMUSCULAIR

Let op
Halvering van de dosis is niet toegestaan. Het effect hiervan op de werkzaamheid is n.l. onbekend, terwijl het niet leidt tot minder bijwerkingen.

Indien de kinkhoestvaccinatie gecontraindiceerd is (zie R.J.F. Burgmeijer en D.J.A. Bolscher "Vaccinaties bij kinderen", 3e herziene druk, Van Gorcum 1998) en in plaats van DKTP, DTP wordt gegeven, dient dagens die de entingverricht, dit duidelijk te vermelden op het oproep kaart (die naar de entadministratie wordt gezonden.

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

FDS 98-223

De minimum leeftijd van de eerste injectie is 7 weken. Er dient minimaal een tussenperiode van 4 weken in acht te worden genomen tussen de drie vaccinaties.
De vierde Hib-injectie wordt bij voorkeur op de leeftijd van 11 maanden gegeven.
Er dient tenminste een tussenperiode van 8 maanden in acht te worden genomen tussen de derde Hib-injectie en de vierde Hib injectie.
Dosering: 0,5 ml INTRAMUSCULAIR.

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

In dient per gevaccineerde zuigeling bekend te zijn in welke ledematen de Hib- en DKTP entingen worden toegediend, in verband met de herkenning van (mogelijke) bijwerkingen.

Indien de beide vaccinaties om één of andere reden niet simultaan worden gegeven, dient men tussen de vaccinaties, ongeacht de volgorde waarin ze worden gegeven, een interval van tenminste 2 weken aan te houden.

- **BMR** (Bot - Mazelen - Rodehond)

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

De BMR-injectie kan op de leeftijd van veertien maanden simultaan met de vierde DKTP- en/of de Hib injectie worden gegeven, waarbij de BMR-, DKTP- en Hib vaccins in verschillende ledematen moeten worden toegediend.

Indien geen gebruik wordt gemaakt van de mogelijkheid om de eerder genoemde vaccinaties samen aan toe te dienen, dient men na de DKTP-enting 2 weken te wachten alvorens met BMR- of Hib-vaccin te enten en na de BMR-enting dient men 4 weken te wachten met toediening van DKTP- of Hib-vaccin.

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

De in 1995 geboren kinderen worden in 1999 gerevaccineerd met DTP vaccin. Afhankelijk van de reeds vroeger gegeven entingen worden 1, 2 of 3 injecties gegeven (zie R.J.F. Burgmeijer en D.J.A. Bolscher "Vaccinaties bij kinderen", 3e herziene druk, Van Gorcum 1998).
Dosering: 1 ml INTRAMUSCULAIR.

2 SCHOOLKINDEREN

Vaccinatieschema

De in 1990 geboren kinderen worden in 1999 gerevaccineerd met DTP-vaccin. Afhankelijk van de reeds vroeger gegeven entingen worden 1, 2 of 3 injecties gegeven; zie ook onder 1.
Dosering: 1 ml INTRAMUSCULAIR.

De in 1990 geboren kinderen krijgen in 1999 een BMR-injectie.
Dosering: 0,5 ml SUBCUTAAN.

De BMR-enting kan simultaan met de DTP-enting worden gegeven; zie ook onder 1.

3 ENTADMINISTRATIES

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

Provincie	Adres	Telefoon	Fax
GRONINGEN	Goreehtkade 8, 9713 GA Groningen	050-3686350	050-3122733
FRIESLAND	Sixmastraat 2, 8932 PA Leeuwarden	058-2880555	058-2880286
DRENTHE	Lauwers 9, 9405 RL Assen	0592 395760	0592 352169
OVERIJSSEL	v. Reeuwijkstraat 50, 7731 EH Ommen	0529-455717	0529-455805
FLEVOLAND	v. Reeuwijkstraat 50, 7731 EH Ommen	0529-455717	0529 455805
GELDERLAND	Korte Cochoornstraat 2, 6811 LB Arnhem	026-4429242	026 4434999
UTRECHT	Zoutkamperschans 7, 3432 TZ Nieuwegein	030-6081316	030 6081517
NRD-HOLLAND	Zeilmakerstraat 40, 1991 JC Velsenbroek	023 5382454	023 5386822
AMSTERDAM	Nieuwe Achtergracht 100, 1018 WT Amsterdam	020-5555460	020 5555760
ZD-HOLLAND	Europaweg 141, 2711 HP Zoetermeer	079 3418238	079-3315047
ROTTERDAM	Schiedamsedijk 95, 3011 EN Rotterdam	010-4339517	010 4339657
ZEELAND	Hollandiaplein 1, 4461 GT Goes	0113 249246	0113-249240
NRD-BRABANT	Bosscheweg 57, 5056 KA Berkel-Enschot	013-5384849	013 5393818
LIMBURG	Dalderhaag 13, 6136 KM Sittard	046-4529910	046 4584479

4 ALGEMEEN

4.1 Organisatie

De uitvoering van het vaccinatieprogramma wordt verzorgd door thuiszorgorganisaties, GGD's en huisartsen, onder medisch toezicht van de artsen van de entadministraties en in overeenstemming met de richtlijnen van de Hoofdinspecteur voor de Gezondheidszorg.

4.2 Vaccindistributie

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

4.3 Registratie en verantwoording

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

4.4 Financiering

De kosten van de uitvoering van het vaccinatieprogramma komen ten laste van die in de A.W.B.Z. geregelde verzekering.
Per verrichte enting wordt een bedrag uitbetaald aan de Provinciale Entadministraties.
De Provinciale Entadministraties zullen volgens landelijke richtlijnen zorgdragen voor doorbetaling van de ter beschikking gestelde gelden aan de meewerkenden aan het vaccinatieprogramma.
Voor vaccinaties in het kader van het Rijksvaccinatieprogramma door de thuiszorg behoeven de ouders geen toegangsbijdrage te hebben betaald. Overigens is per 1-1-1999 de toegangsbijdrage voor de thuiszorg afgeschaft.

4.5 Kinderen tot 13 jaar die niet of niet volledig zijn ingeënt volgens het voor die jaarklasse geldende entschema, kunnen de nog **noodzakelijke** entingen kosteloos ontvangen in het kader van het vaccinatieprogramma.
Dit geldt uitsluitend voor de DKTP-, DTP- en BMR-entingen.
Voor de Hib-entingen geldt dat in het kader van het vaccinatieprogramma alleen kinderen geboren vanaf 1 april 1993 voor vaccinatie in aanmerking komen.

4.6 De Gemeentelijke Gezondheidsdiensten van Amsterdam en Rotterdam zijn wat betreft de administratieve verzorging van het vaccinatieprogramma gelijkgesteld met de Provinciale Entadministratie.

Appendix 3 Package Insert DKTP

RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEU

BILTHOVEN-NEDERLAND

040004

Difterie-, Kinkhoest-, Tetanus-, Poliomyelitisvaccin

Samenstelling

1 dosis (1 ml) bevat:

difterietoxoid	≥ 30	IE *
kinkhoestvaccin	4	IE
tetanustoxoid	≥ 60	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	25	µg

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

Farmaceutische vorm en presentatie
Difterie-, Kinkhoest-, Tetanus-, Poliomyelitisvaccin (DKTP) vaccin is een suspensie voor injectie en wordt afgevuld in:
flesjes à 1 ml (1 dosis) bestelnr. 360.1

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

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 één 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 optrad: hoge koorts, aanhoudend, ontroostbaar huilen, collaps of een op shock gelijkende toestand (episoden van bleekheid, hypotonie en hyporespons), convulsies (met of zonder koorts) kunnen volgende doses vaccins die de pertussis component bevatten in principe worden gegeven, maar kunnen aanvullende adviezen nodig zijn (bijvoorbeeld koortswering).

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

Géén contra-indicatie zijn:
- een voorgeschiedenis van met koorts gepaard gaande convulsies en in de familie voorkomende stuipachtige 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 corticosteroïden gegeven, gedoseerd 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 geïnactiveerd 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 één maand, en dient vóór de leeftijd van 6 maanden te zijn voltooid voor een tijdige bescherming. De eerste revaccinatie ("DKTP-4") wordt tenminste 6 maanden na de laatste enting van de primaire serie gegeven. Met name ook prematuur geboren kinderen volgen dit schema volgens de kalenderleeftijd, zonder correctie voor de te vroege 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 bevriezing is het vaccin onbruikbaar.

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

Appendix 4 Package Insert DTP

RIJKSINSTITUUT
VOOR VOLKSGEZONDHEID
EN MILIEU

040013

Difterie-, Tetanus-, Poliomyelitisvaccin

Beschrijving en samenstelling
DTP vaccin is een gecombineerd vaccin tegen difterie, tetanus en poliomyelitis.
Difterie- en tetanustoxoïde zijn bereid uit toxines geproduceerd door respectievelijk Corynebacterium diphtheriae, stam Parke Williams nr. 8 en Clostridium tetani, stam Harvard 49205. De poliomyelitiscomponent 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:

difterietoxoïde	≥ 5	IE *
tetanustoxoïde	> 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	0,025	mg

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

Farmaceutische vorm en presentatie
DTP vaccin is een suspensie voor injectie en wordt afgeleverd 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 gezwenkt 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
Eén 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 DKTP 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.

December 1997

Appendix 5 Package Insert Hib

RIJKSINSTITUUT
VOOR VOLKSGEZONDHEID
EN MILIEU

Haemophilus b conjugaat (PRP-T) vaccin

Haemophilus influenzae type b conjugaat vaccin gevriesdroogd

Geproduceerd door Pasteur Mérieux [illegible] - Lyon - France

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 tetanustoxoïd als drageneiwit. Het vaccin wordt geresuspendeerd met de bijgepakte reconstitutievloeistof (0,4 % natriumchloride oplossing).

Het gevriesdroogde vaccin bevat:
- polysaccharideconjugaat met tetanustoxoïd (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 evenveel 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 elke 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 corticosteroïden 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 micro-organismen.
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 intramusculair 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 6 Package Insert BMR

RIJKSINSTITUUT
VOOR VOLKSGEZONDHEID
EN MILIEU

040025

Bof-, Mazelen-, Rubellavaccin

levend, gevriesdroogd

Beschrijving en samenstelling
Bof-, mazelen-, rubellavaccin (BMR vaccin) is een gevriesdroogd preparaat van levend, verzwakte bof-, mazelen- en rode hond (= rubella) virussen.
Bofvirus, stam Jeryl Lynn, is gekweekt op kippenembryofibroblasten; mazelenvirus, stam Moraten, is gekweekt op kippenembryofibroblasten en wordt verkregen door de reeds verzwakte Edmonston stam door herhaalde passage in celculturen verder te verzwakken en rubellavirus, stam Wistar RA27/3, is gekweekt op menselijke diploide celculturen (WI-38).

1 dosis (0,5 ml) bevat na resuspensie met de bijgepakte reconstitutievloeistof:
bofvirus ≥ 5000 p.f.u.*
mazelenvirus ≥ 1000 p.f.u.
rubellavirus ≥ 1000 p.f.u.
Sorbitol en gehydrolyseerde gelatine zijn als stabilisatoren aan het vaccin toegevoegd.
Het vaccin bevat geen antibiotica en geen conserveermiddel.

*) p.f.u. = plaque forming unit

Farmaceutische vorm en presentatie
BMR vaccin is een poeder voor injectievloeistof en wordt afgevuld in:
flesjes à 1 dosis, met even zoveel flesjes reconstitutievloeistof bestelnr. 442

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

RVG nummer
BMR vaccin is in het register ingeschreven onder RVG-nummer 17654.

Indicatie
Actieve immunisatie tegen bof, mazelen en rubella vanaf de leeftijd van 14 maanden.
In het Rijksvaccinatie programma (RVP) wordt BMR vaccin tweemaal gegeven; vanaf de leeftijd van 14 maanden en in het 9de levensjaar.

Contra-indicaties
- BMR vaccin bevat levende verzwakte virusstammen en toepassing is dan ook gecontraindiceerd bij patiënten die met corticosteroïden of cytostatica worden behandeld en bij patiënten met stoornissen in het afweermechanisme waaronder HIV-geïnfecteerde patiënten met ernstige immuundeficiëntie (zie ook Speciale waarschuwingen en voorzorgen bij gebruik).
- BMR vaccin is eveneens gecontraindiceerd bij zwangerschap.

branderig, stekend gevoel geven op de plaats van enting.
Koorts en/of erytheem kan optreden 5 tot 12 dagen na vaccinatie. Kinderen die met hoge temperatuur op vaccinatie reageren, kunnen, indien hiertoe gepredisponeerd, een febriele convulsie krijgen.

In zeer zeldzame gevallen zijn na vaccinatie encefalitis en andere reacties van het centraal zenuwstelsel waargenomen. Een oorzakelijk verband met vaccinatie kon daarbij niet worden uitgesloten; echter een verhoging van het aantal gevallen in vergelijking met niet-gevaccineerden is niet waargenomen. De rubella-component van het vaccin geeft bij kinderen weinig reacties. Soms wordt een zwelling van de cervicale of occipitale lymfeklieren waargenomen. Echter, vooral bij volwassen vrouwen, zijn 2 à 4 weken na vaccinatie passagère arthralgieën en arthritiden gezien.
Sporadisch treden allergische reacties op. Artsen wordt verzocht mogelijke bijwerkingen te melden aan de afdeling Klinisch Onderzoek van het Laboratorium voor Veldonderzoek Vaccins van het RIVM, tel. 030-2742424.

Bewaring
Het produkt dient bij 2 - 8 °C te worden bewaard; beschermen tegen licht.
Geresuspendeerd vaccin wordt bij voorkeur direct gebruikt. Eventueel kan het vaccin na reconstitutie, mits nog in het flesje (en dus niet in spuit) teruggeplaatst in het donker bij 2 - 8 °C tot maximaal 4 uur worden bewaard.
Resterend vaccin dient te worden vernietigd b.v. door koken in water gedurende 10 minuten.

Uiterste gebruiksdatum
De achter exp. aangegeven datum is de uiterste gebruiksdatum. Het produkt mag na deze datum niet meer worden gebruikt.

Appendix 7 Package Insert MMR

DENOMINATION ET GROUPE

M-M-R® VAX

(VACCIN VIVANT CONTRE LA ROUGEOLE, LES OREILLONS ET LA RUBÉOLE, MSD)

[illegible]

NOTE À L'INTENTION DES MEDECINS

[illegible]

INDIQUE DANS

[illegible]

Remarques particulières

[illegible]

COMMENT L'UTILISER ET EN QUELLE QUANTITE

[illegible]

CAS OU L'USAGE DU MEDICAMENT DOIT ETRE EVITE

[illegible]

EFFETS NON DESIRES

[illegible]

PRECAUTIONS PARTICULIERES

[illegible]

UTILISATION EN CAS DE GROSSESSE ET D'ALLAITEMENT

[illegible]

INTERACTIONS AVEC D'AUTRES MEDICAMENTS OU DES ALIMENTS

[illegible]

FORMES, VOIES D'ADMINISTRATION, CONDITIONNEMENT ET MODE DE DELIVRANCE

[illegible]

CONSERVATION

[illegible]

COMPOSITION

[illegible]

TITULAIRE D'ENREGISTREMENT / **FABRICANT**

[illegible]

BENAMING EN GROEP

M-M-R® VAX

(LEVEND MAZELENVIRUS-, BOFVIRUS- EN RUBELLAVIRUS-VACCIN, MSD)

[illegible]

AANGEWEZEN BIJ

[illegible]

Bijzondere overwegingen

[illegible]

INENTING VAN HALF-VOLWASSEN EN VOLWASSEN VROUWEN, DIE NIET ZWANGER ZIJN, MET HET VACCIN TEGEN RODEHOND - DOOR MIDDEL VAN HET GECOMBINEERDE VACCIN (M-M-R VAX) OF DOOR MIDDEL VAN HET VACCIN TEGEN RODEHOND ALLEEN.

[illegible]

HOE GEBRUIKEN EN HOEVEEL

[illegible]

OMSTANDIGHEDEN WAARBIJ HET GEBRUIK VAN HET GENEESMIDDEL MOET WORDEN VERMEDEN

[illegible]

ONGEWENSTE EFFECTEN

[illegible]

[illegible]

REGISTRATIEHOUDER
PASTEUR MÉRIEUX MSD
[illegible]
1140 Brussel
Tel. 02/726 95 84

FABRIKANT
MERCK SHARP & DOHME B.V.
Postbus 581
NL-2003 PC Haarlem
Nederland

BEZEICHNUNG UND GRUPPE

M-M-R® VAX

LEBENDVAKZINE GEGEN MASERN, MUMPS UND RÖTELN, (MSD)

Gruppe: Vakzine gegen Masern, Mumps und Röteln

Hinweis für Ärzte

[illegible]

ANWENDUNGSGEBIET

[illegible]

Dieser Impfstoff kann auch bei Erwachsenen angewandt werden.

[illegible]

Pasteur Mérieux MSD