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

Numbers V - Reports in 1998

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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. Additional data are obtained, if necessary, from parents, general practitioner, paediatrician etc. After supplementation and verification of data a (working) diagnosis is made and causality assessed. In this report on 1998 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 1100 AEFI were submitted. Of these 1.5% (16) was unclassifiable because of missing information. In 80% (877) of the classifiable events a possible causal relation with vaccination was established and in 18% (197) the events were judged to be coincidental. Compared to 1997 there was again a rise in the number of notifications. This increase is thought to be due to decreased underreporting, increased awareness and apprehension and possibly also to some increase in true side effects, mainly fever associated events and crying.

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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
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	Netherlands 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. 98% Van de spontane meldingen komt telefonisch binnen, in hoofdzaak vauit de Jeugdgezondheidszorg (81.5%). Nadere gegevens van anderen dan de melder, bijvoorbeeld van ouders, huisarts of ziekenhuis worden in circa 66% 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 (96%) 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 verdere afname in aantal. 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 vijfde jaarrapport.
In 1998 zijn 1100 meldingen binnengekomen, betreffende 1065 kinderen, op een totaal van meer dan 2 miljoen vaccinaties per jaar. 16 meldingen (1.5%) waren niet te beoordelen wegens het ontbreken van informatie. Drie van deze meldingen waren mogelijk ernstig. 80% (887) van de meldingen werd als bijwerking beoordeeld met een mogelijk, waarschijnlijk of zeker causaal verband. Een toevallige samenloop werd aangenomen in 18% (197) van de meldingen.
Van de milde algemene, huid- of lokale verschijnselen (534) werden 384 (72%) meldingen als mogelijke bijwerking uitgeboekt in 1998.
Verkleurde benen (in 1995 voor het eerst afgesplitst van de huidverschijnselen) werden 125 keer gemeld, met in op twee na alle gevallen een mogelijke causale relatie.
Andere ernstige of heftige postvaccinale gebeurtenissen (gerubriceerd onder convulsies, collaps, "ziek major", lokaal major, persistent screaming en de sterfgevallen) werden 441 keer gemeld en in 82% (363) beoordeeld als mogelijke bijwerking. Collaps, waaronder ook atypische en onvolledige episodes, werd 158 maal gediagnosticeerd, met slechts in vijf gevallen geen oorzakelijk verband. Daarnaast enkele keren Breath-Holding-Spells (4) en flauwvallen (12) in oudere kinderen. In 1998 werden 65 convulsies gemeld, waarvan 61 febriel, waarvan 54 als bijwerkingen werden beoordeeld. De 65 atypische aanvallen (54% met koorts) hadden in 85% een mogelijk causaal verband. Epilepsie (3) werd niet als bijwerking beoordeeld, maar als een coïncidentie. Op een na alle meldingen van persistent screaming (29) werden gezien als bijwerking. Koorts van $\geq$40.5°C was de werkdiagnose bij 52 kinderen uit de "ziek major" groep, in 92% als bijwerking beoordeeld, en nog eens 8 maal als onderdeel van een ander ziek major beeld. In de andere rubrieken waren er nog 36

kinderen met hoge koorts, vooral bij de koortsstuipen. Van de 33 andere beelden uit de "ziek major" groep was er 11 keer een mogelijk causaal verband, artritis (1), hemibeeld (nno,1), vaccinitis (2) myoclonieen (1), abducens parese (1) cerebellaire ataxie (1), hypoglykemie (1) en ITP (3). De overige 22 waren coïncidenteel. Er waren negen abcessen (waarvan twee na BCG), in geen van de gevallen gekweekt, en 6 anderszins heftige lokale reacties. De vijf sterfgevallen in 1998 gemeld, zijn na uitgebreide evaluatie als toevallige samenloop beoordeeld, met andere oorzaken.
De meeste meldingen betroffen DKTP en Hib vaccinaties (853). BMR was betrokken in 170 gevallen, waarvan 32 maal gecombineerd met andere vaccins. In 50% was er een mogelijke causale relatie. Voor de andere vaccin(combinatie)s was dit percentage 85%. Vergeleken met 1997 was er een stijging van het aantal meldingen van 34%. Deze toename gold alle vaccindoses in min of meer gelijke mate. Analyse maakt waarschijnlijk dat zowel verdere afname van de onderrapportage als verhoogde aandacht voor en bezorgdheid over mogelijke bijwerkingen een rol speelden. Daaraast ook mogelijk enige werkelijke toename van bijwerkingen na DKTP/Hib vaccinaties, met name van met koorts gepaard gaande beelden en huilen.

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. 98% Of reports come in by telephone, in majority from Child health Clinic staff (81.5%). Parents, GP's and/or hospital provide additional data on request (66% 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 (96%). 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 1998, on a total of over 2 million vaccinations, 1100 AEFI were submitted, concerning 1065 children. Of these only 1.5% (16) were not classifiable because of missing information (all were minor events). 80% (887) of classifiable events were judged to be possibly, probably or definitely causally related with the vaccination and 18% (197) of the events were coincidental. Minor skin, local or systemic symptoms were registered in 534 cases of which 384 (72%) were classified as possible adverse reactions. Discoloured legs were reported 125 times with a causal relation more or less likely in all but two cases. Other major adverse events (categorised under convulsions, collapse, persistent screaming and general major illness and death) occurred in 441 cases of which 82% (363) a possible adverse reaction. All five death cases were considered chance occurrences with other causes.

Collapse, including atypical and incomplete episodes, was diagnosed 158 times, in five cases with no causal relation. Four times breath holding spells and twelve times fainting in older children were reported. Convulsions were diagnosed in 65 cases, 61 of which were febrile, in 54 with inferred causality. Atypical attacks (54% with fever) were diagnosed 65 times, of which 85% with a possible causal relation. Epilepsy (3) was not considered causally related with the vaccinations. In all but one of the 29 cases persistent screaming was considered to be an adverse reaction.

Fever $\geq$40.5°C was present in 52 cases of the major illness group, 92% of cases with inferred causality. Another 36 times was high fever part of another specific event, mainly febrile convulsions. Of the other 33 major illness cases 11 had a possible causal relation, arthritis (1), hemiparesis (1) , vaccinitis (2), myoclonics (1), abducens paresis (1), cerebellar ataxia (1), hypoglycaemia (1) and ITP (3). The other 22 were considered to be unrelated. There were nine abscesses (two after BCG), with no culture taken, and 6 other major local reactions.

Most frequently reports involved DPTP and Hib vaccinations (853). MMR was involved 170

times, 32 times with simultaneous other vaccines. In 50% of cases there was a possible causal relation with MMR. For the other vaccine combinations this percentage was 85%. Compared to 1997 the number of reports rose with 34%. This increase was more or less the same for the different vaccine doses. After thorough evaluation this appears to be due both to further decrease in underreporting as to increased awareness and apprehension about possible side effects. Also possibly there is some true increase in adverse reactions after DPTP/Hib, mainly events with fever and crying.

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 1998 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 in December 1997 the combined DPTP vaccine contained a better defined pertussis component with on average a higher potency in the mouse protection test. We will discuss some specific adverse events and their relation to the vaccination. Special attention will be given to underreporting and contra-indications and to management of adverse events. 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]. Also there has been on and off disquiet about vaccines and childhood vaccinations[13,14,15,16,17,18]. 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[7,19,20].

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]. 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 Netherlands Vaccination Programme

3.1 Vaccines and Schedule

In the Netherlands mass vaccinations of children were undertaken from 1952 onwards, with institution of the National Vaccination Programme (RVP) in 1957. From the start all vaccinations covered, were free of charge and have never been mandatory. Although a law existed on smallpox vaccinations, this law has never been enforced. With the eradication of smallpox vaccinations were abandoned and this law was revoked in 1978[25,26]. 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 1998 is included in box 1 (appendix 2).

Box 1. Schedule of the National Vaccination Programme of the Netherlands in 1998

3 months	DPTP1 + Hib1
4 months	DPTP2 + Hib2
5 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 3-6). 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[25]. 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 3, 4, 5 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[25].
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.

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)[25]. 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[27]. 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 circumference 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%[28]. (the accurate numbers on birth cohorts 1997 and 1998 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[25]. 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, 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 Netherlands 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[7,29]. 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)[20,30,31].

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 24h-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. This requires adequate knowledge of epidemiology, child health, immunology, etiology and differential diagnoses in paediatrics.

Box 5. Points of consideration in appraisals of causality

- 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

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 $\geq$38.5°C it is booked as febrile convulsion unless the convulsion is symptomatic for meningitis or for other illness. Febrile seizures of more than 15 minutes or asymmetrical or recurring within 24 hours are complex as opposed to simple (classic). Definite epileptic 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 there must be 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 and 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 (SOP 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 1998 LVO-RIVM received 1082 notifications of adverse events, on a total of over 2 million vaccinations. (birth cohort 1998, 199.408; CBS per may 2000) The notifications involved 1065 children. Of these 26 had multiple reports, concerning two different vaccination dates (12 in 1996 and 14 in 1997). Nine reports were compound with two distinct adverse events concerning one vaccination date (10 in 1996 and 7 in 1997). These AE are listed under the respective event categories. As described in paragraph 4.2, notifications of adverse events concerning more than one vaccination date with only mild or common symptoms were booked as single reports unless reported on different dates (table 1). This annual report contains 1100 reported adverse events.

Table 1. Types of reports of notified AEFI in 1998

notifications	children	adverse events
single	1030	1030*
multiple	26	52
compound	9	18
total	1065	1100

* 14 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.

Table 2. Number of reported AEFI per year

year of notification	written assessments[1]	total[2]
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

[1] before 1994 registration according to year of vaccination; from 1994 registration according to year of notification

[2] 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 not consistent with random fluctuations (or time trends). As in previous years the notification rate is not even over the months, range 71-114 with the lowest rate in May and August and lacking the usual low in winter.
Criteria for formal written assessment changed in 1996; this has had influence on the year of report, with less written assessments. See paragraph 6.5.

6.2 Reporters

The first person to notify LVO-RIVM about an adverse event is regarded as the reporter. As in previous years the vast majority of reports were made by telephone. Only 25 (2.3%) notifications came by regular mail, most frequently as (hospital discharge) letter, and some on regionally used, special report forms. Over the last five years this number fluctuates a little between 25 en 51. Reports from Child Health Clinics accounted for 81.5% of the total number with an increasing share of reports by the nurse.
The other notification sources were more or less stable (table 3).

Table 3. Source and reporting route of AEFI in 1998

		1993	1994	1995	1996	1997	1998	tel.	mail
Clinic staff	Physician	341	474	548	466	547	678	659	19
	Nurse	40	78	102	116	142	219	215	4
Paediatrician		54	60	59	56	39	69	68	1
General Practitioner		27	25	13	26	20	35	34	1
School Health Service		23	15	18	17	10	31	31	-
District Consultant		-	9	18	11	16	15	15	-
Parent		11	25	34	35	40	52	52	-
Other		-	5	6	2	7	1	1	-
Unknown		-	21	2	3	1	-	-	-
Total		496*	712	800	732	822	1100	1075	25

* estimate

The parents of 52 (4.7%) children reported directly themselves; mostly they were advised to do so by the clinic staff. This percentage of parent reports is comparable to 1997 (4.9%) and 1996 (4.8%). But absolute numbers increased from 25 in 1994 to 52 in 1998.

6.3 Regional Distribution

Reports come from all over the country, but are not evenly spread. Standardisation of the rate per 1000 vaccinated infants shows that only the three big cities (Den Haag, Amsterdam, Rotterdam) differ significantly from the country's average of 5.9/1000 for the year under report. This does not have very much impact in absolute numbers, since these areas do not have large populations. Applying the country's average to these regions will mean approximately 25 reports less or ten reports more. In all but one region (Rotterdam) the reporting rate increased. See table 4 and figure 1.

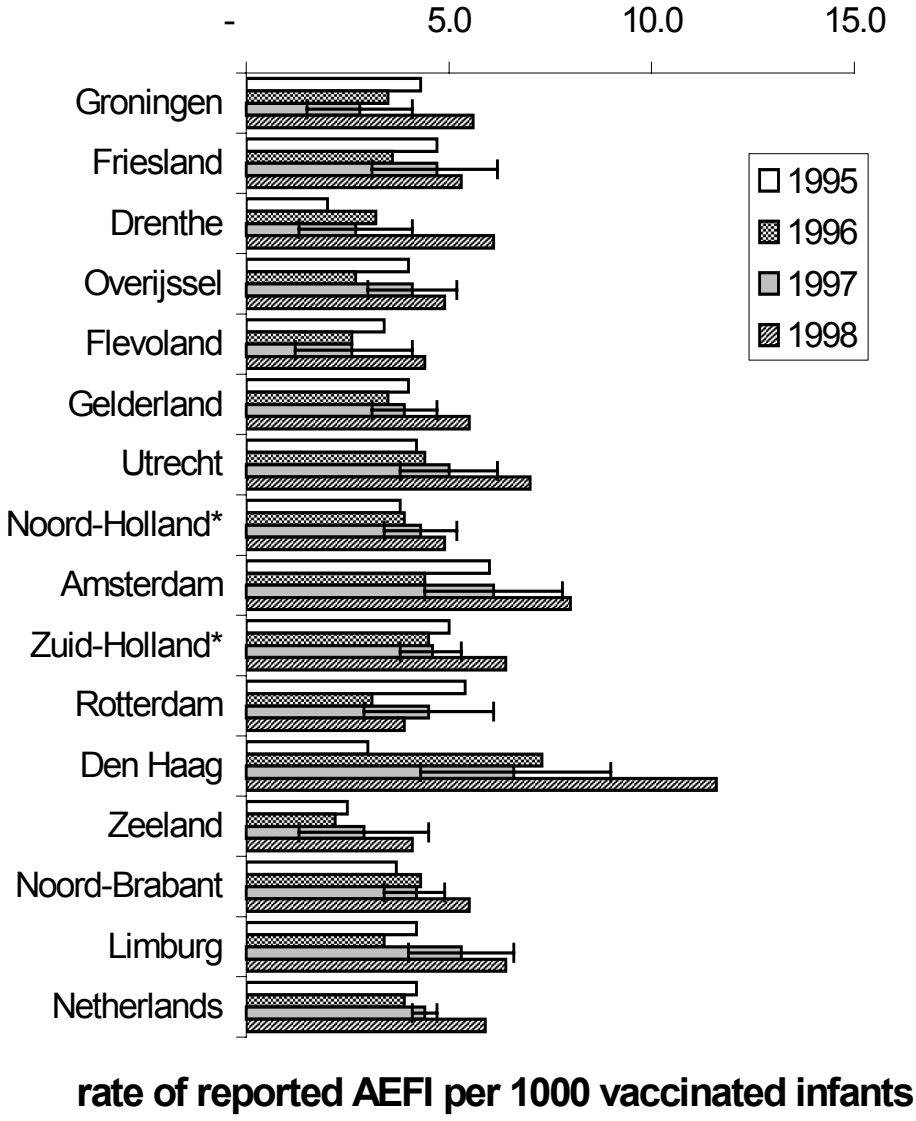

Figure 1. Number of reported AEFI in 1995 to 1998 per 1000 vaccinated infants

Table 4. Regional distribution of reported AEFI in 1993-1998, per 1000 vaccinated infants[d]

	1993	1994	1995	1996	95% c.i. [a]	1997	95% c.i. [a]	1998	95% c.i. [a]
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
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
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
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
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
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
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
Noord-Holland[b]	1.7	2.4	3.8	3.9	3.1-4.7	4.3	3.4-5.2	4.9	4.0-5.9
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
Zuid-Holland[b]	3.3	4.6	5.0	4.5	3.7-5.2	4.6	3.8-5.3	6.4	5.4-7.3
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
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
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
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
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
Netherlands [c]	2.6	3.6	4.2	3.9	3.6-4.2	4.4	4.1-4.7	5.9	5.5-6.2
range	0.5-7.0	1.2-8.2	2.0-6.0	2.2-7.3		2.6-6.6		3.9-11.6	

[a] proportionate confidence interval
[b] provinces without the three big cities (Amsterdam, Rotterdam, Den Haag)
[c] the Netherlands have a birth cohort of approximately 200.000 per year and coverage of 97% on average
[d] for 1997 and 1998 figures of cohort 1996 are used since IGZ has not yet published coverage over cohorts 1997 and 1998

6.4 Vaccines

In 1998 most notifications were about recent vaccinations, all except 34. These latter notifications arose from concerns about planned booster vaccination or vaccination of younger siblings, in majority MMR (18) and 4 year booster dose D(P)TP (6). As in prior years, reports on the first simultaneous DPTP+Hib vaccinations were the most prevalent (372), with declining numbers on subsequent doses and older age, respectively 205, 148, 148 for second, third and fourth dose (table 5). Only 22 times DPTP was given singly, without simultaneous other vaccines. Two reports concerned single HepB vaccination. Four children received DTP(olio) instead of the scheduled DPTP, twice because of perceived contra-indication or parental choice and two vaccinees were late starters (on philosophical grounds). In 1998 MMR was involved 170 times of which 141 concerned MMR1 (once before the age of one year) in four cases with simultaneous other vaccines. 29 Reports were about MMR2 in all but one with simultaneous DTP. Twice there was a late report about single measles vaccine, in use up till 1987.

DTP revaccination at 4 years of age was involved 31 times, once with simultaneous Hib and once with MMR1; three children got DPTP revaccination on indication twice because of special risk factors for pertussis and once because of catch up schedule (with Hib and MMR1). Reports concerned revaccination at school age 33 times, of which once only MMR and four times only DTP.

Table 5. Schedule and vaccines of reported AEFI in 1998

vaccine given⇒ scheduled ⇓	dptp	dptp hib	hib	dptp hib mmr	dptp mmr	mmr	dtp	dtp hib	dtp mmr	hepb	bcg	flu	other	total 1998	1997	1996	1995	1994
dptp1+hib1	7	365[a]	-	-	-	-	-	-	-	-	-	-	-	372	323	284	324	300
dptp2+hib2	1	203	1	-	-	-	-	-	-	-	-	-	-	205	143	139	141	126
dptp3+hib3	3	143[b]	1	-	-	-	-		-	-	-	-	1[p]	148	103	96	103	91
dptp4+hib4	5	134[c]	1[k]	1	1[f]	-	2[i]	2[j]	-	1	-	-	1[o]	148	95	88	83	70
dose?	4	8	1[l]	-	-	-	-	-	-	1	-	-	-	14	7	4	9	2
mmr1	-	-	-	-	-	137	-	-	-	-	-	-	2[n]	139	97	80	95	74
dtp5	2[e]	-	-	1[d]	-	-	29[g]	1[h]	1[q]	-	-	-	-	34	22	24	18	11
dtp6+mmr2	-	-	-	-	-	1	4	-	28	-	-	-	-	33	25	13	21	21
hib catch-up	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	8
other	-	-	-	-	-	-	-	-	-	-	3	2	2[m]	7	7	4	3	9
total	22	853	4	2	1	138	35	3	29	2	3	2	6	1100	822	732	800	712

[a] once with hepb vaccine
[b] twice with hepb vaccine
[c] once dptp1/hib1 late start refugee
[d] dptp3/hib/mmr1 catch up dose
[e] children with special indication, at high risk for pertussis
[f] second dtpt catch up dose of refugee
[g] once second dose refugee
[h] hib catch up dose
[i] first dose late starters
[j] once because of perceived contraindication and once parental choice
[k] first catch up dose late starter
[l] whole hib series
[m] twice late reports of single measles vaccine
[n] tetanus in 14 year old child and menB3 in trial in 8 year old
[o] opv in child with epilepsy,
[p] dkt+opv administered in other country
[q] dtp5 with catch up dose mmr1

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. Fits, especially febrile convulsions, are reported more often after the fourth DPTP/Hib and the first MMR. No children with anaphylactic shock were reported and no cases of encephalopathy. See for details the paragraphs of the specific event categories (paragraph 6.9).
Compared to 1997 the increase in reports is 34%. It seems to be an overall increase for the different vaccines with for DPTP/Hib doses combined a 32% increase and for the other vaccines 41%, much lower in total number however.
Over the different vaccine doses of DPTP/Hib (and MMR1) the increase in absolute numbers is comparable, but relatively the increase is larger with increasing dose number/age. The relative frequencies of reported AEFI over the different vaccines however, are comparable in the listed years (figure 2). There is a slow minor decrease in the relative frequency of reported events after the first vaccinations, more or less compensated with increase in reports after the next doses.

Table 6. Event category and (scheduled) vaccine dose of reported AEFI in 1998

vaccine⇒* / event ⇓		first	dptp second	+ third	hib fourth	dose?	mmr1	dtp5	mmr2/ dtp6	other	total 1998	1997	1996	1995	1994
local reaction		12	11	8	12	4	1	8	10	3	69	48	46	39	31
general illness	minor	117	81	60	54	6	61	11	13	2	405	254	244	280	242
	major	16	16	8	18	2	22	3	-	-	85	57	52	55	61
persistent screaming		16	7	6	-	-	-	-	-	-	29	26	16	22	37
skin symptoms		13	13	8	10	2	19	4	6	-	75	76	61	61	78
discoloured legs		66	41	11	7	-	-	-	-	-	125	94	96	93	43
faints		107	28	20	5	-	2	7	4	1	174	155	134	147	141
fits		23	7	27	42	-	32	1	-	1	133	108	73	97	74
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		-	-	-	-	-	-	-	-	-	-	1	1	1	-
death		2	1	-	-	-	2	-	-	-	5	3	9	5	5
total		372	205	148	148	14	139	34	33	7	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 local reactions but more in absolute numbers in general illness category, convulsions and discoloured legs. For MMR1 the increase is in the general illness category mainly, with the number under fits more or less stable. See for specifics the respective event categories under paragraph 6.9.
In the numbers in the tables all reported events are included irrespective of causality. See for degree of causality, paragraph 6.8, and 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). For minor illness the 36.8 % of 1998 is a little above the range of the four previous years and the 6.9% for skin symptoms and discoloured legs a little below that range. For collapse reactions the relative frequency is far below the range of 1994-1997, there was a small increase in absolute numbers for this event as well however.

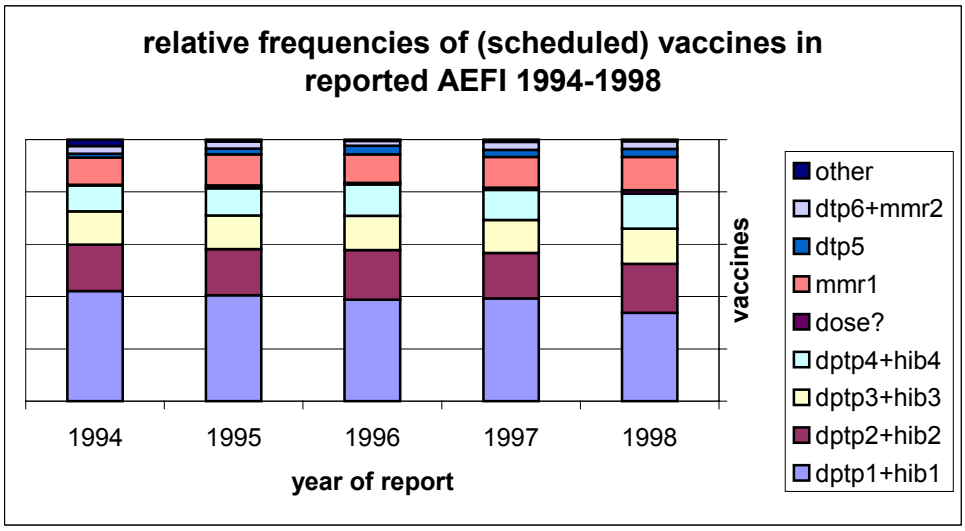

Figure 2. Relative frequencies of involved vaccines in reported AEFI 1994-1998

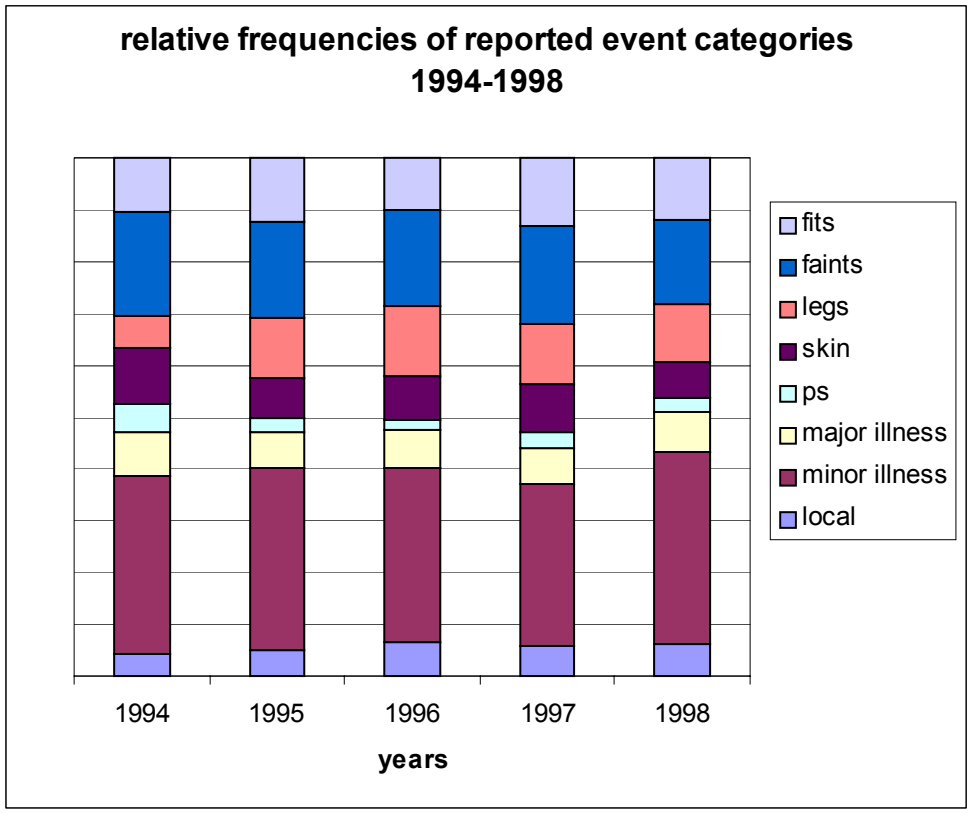

Figure 3. Relative frequencies of events in reported AEFI 1994-1998.

6.5 Feedback to Reporters

Feedback of diagnosis and causality assessment with advice about further vaccinations is a major characteristic of the surveillance system. This feedback is increasingly by telephone due to a change in procedures. In 1995 29% of reports got a full written account declining in subsequent years, 19%, 9% and 4% in 1996, 1997 and 1998 respectively (table 7).

Table 7. Feedback method and events of reported AEFI in 1995-1998

event ⇓ feedback method⇒		written	tel.	1995 total	written	tel.	1996 total	written	tel.	1997 total	written	tel.	1998 total
local reaction		5	34	39	7	39	46	-	48	48	-	69	69
general illness	minor	59	221	280	21	223	244	3	251	254	4	401	405
	major	25	30	55	17	35	52	16	41	57	14	71	85
persistent screaming		3	19	22	1	15	16	-	26	26	-	29	29
skin symptoms		9	52	61	8	53	61	4	72	76	1	74	75
discoloured legs		13	80	93	13	83	96	4	90	94	1	124	125
faints		56	91	147	36	98	134	20	135	155	9	165	174
fits		58	39	97	29	44	73	25	83	108	14	119	133
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		1	-	1	1	-	1	1	-	1	-	-	-
death		5	-	5	8	1	9	3	-	3	5	-	5
total		234	566	800	141	591	732	76	746	822	48	1052	1100

6.6 Source of Information and Medical Intervention

In a little over one third of the notifications the reporter was the sole informant, in 66% information was received from others also (table 8). In 95% the clinics (child health care, school health and refugee clinics) supplied information. Parents were in 62% (687) of cases contacted and sole informer of 21 reports. For 1997, 386 parents (47%) were contacted and 24 times the parents were the sole informer.
Hospital specialists supplied information in 15% of the reports as in 1997, meaning an increase of 42 in actual numbers.

Table 8. Information sources and events of reported AEFI 1998

																total
info ⇒	clinic[a]	+	+	+	+	+	+	+	+	-	-	-	-	-	-	1049
	parent	-	+	+	+	+	-	-	-	+	+	+	-	-	-	687
	gen. pract.	-	-	-	+	+	-	+	+	+	-	-	+	-	-	59
	hospital	-	-	+	-	+	+	-	+	-	+	-	-	+	-	168
event ⇓	unknown	-	-	-	-	-	-	-	-	-	-	-	-	-	+	2
local reaction		33	27	1	3	-	1	1	-	1	-	1	-	-	1	69
general illness	minor	150	187	16	7	1	15	5	-	2	1	12	5	3	1	405
	major	27	31	12	-	4	4	-	2	-	-	2	-	3	-	85
persistent screaming		13	15	-	-	-	-	-	-	-	-	-	-	1	-	29
skin symptoms		27	34	-	1	-	2	2	1	-	-	3	3	2	-	75
discoloured legs		33	81	5	2	-	3	-	-	-	-	-	-	1	-	125
faints		27	103	26	3	3	6	2	2	-	-	-	-	2	-	174
fits		13	65	28	3	3	12	1	1	-	-	3	1	3	-	133
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-it is		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
death		1	-	1	-	-	2	-	1	-	-	-	-	-	-	5
total		324	543	89	19	11	45	11	7	3	1	21	9	15	2	1100

[a] child health , school health and refugee clinic
[b] twice medical consultant of vaccine registry

The impact of adverse events may also be illustrated by medical intervention received. In 28% (311) of reported events no professional medical help was sought or was not recorded by us and in 13% of reports parents (140) administered medication: paracetamol suppositories or diazepam by rectiole for instance. Nearly 60% of the parents contacted the clinic or GP, called the ambulance, or went to hospital, with 10 % admittance. In 1997 these latter percentages were 52% and 11%. In table 9 intervention is ordered according to highest level used.

Table 9. Medical intervention and events of reported AEFI in 1998

event⇓ intervention⇒	?	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	21	6	4	12	3	20	-	3	-	-	-	-	69
general illness minor	101	32	66	27	33	84	-	28	6	22	6	-	405
major	13	1	11	-	7	20	-	7	2	22	2	-	85
persistent screaming	5	6	8	4	2	3	-	1	-	-	-	-	29
skin symptoms	21	2	4	11	2	23	-	11	1	-	-	-	75
discoloured legs	27	13	27	9	12	27	-	4	1	4	1	-	125
faints	18	26	15	16	16	44	-	12	6	21	-	-	174
fits	14	3	5	1	13	34	10	5	10	38	-	-	133
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	-	-	-	-	-	-	-	-	-	-
death	1	1	-	-	-	-	-	-	-	-	-	3	5
total	221	90	140	80	88	255	10	71	26	107	9	3	1100

[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, slowly decreasing in the last four years from the 60% in 1994 en before (table 10). Distribution over the different events ranged from 51% (collapse) to 59% boys (skin) with events with less than 30 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 1997 and 1998

event ⇓ sex⇒	male	female	unknown	1997 total	male	female	unknown	1998 total
local reaction	22	25	1	48	33	31	5	69
general illness minor	141	106	7	254	209	185	11	405
major	33	24	-	57	49	36	-	85
persistent screaming	10	16	-	26	19	10	-	29
skin symptoms	47	29	-	76	40	29	6	75
discoloured legs	41	53	-	94	69	55	1	125
faints collapse	84	60	1	145	80	77	1	158
BHS	4	-	-	4	2	2	-	4
fainting	2	4	-	6	6	5	1	12
fits convulsions	31	27	-	58	34	31		65
epilepsy	3	2	-	5	1	2	-	3
atypical attacks	24	19	2	45	37	28	-	65
anaphylactic shock	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	1	-	1	-	-	-	-
death	-	3	-	3	2	3	-	5
total	442	369	11	822	581	494	25	1100

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 1998 in 80% of reports were considered adverse reactions, equal to 1997. The other events were considered coincidental events with improbable or absent causal relation with the vaccinations. 16 Notifications were not classifiable (1.5%). There are great differences in causality over the different event categories. On the one end persistent screaming with in (nearly) 100% a more or less likely causality and on the other extreme the children who died, where there was judged to be no causal relation with the vaccinations in all instances. For MMR vaccination only 50% of reported adverse events were considered an adverse reaction in 1998. For DTP, DPTP and Hib vaccinations this percentage was 88.4%. For 1997 these percentages were 53% (MMR) and 80% (DTP, DPTP and Hib). See for further specifics the event categories below (paragraph 6.9).

Table 11. Causality and events of reported AEFI in 1998

event ⇓	causality⇒	certain	probable	possible	improbable	non classifiable	total
local reaction		46	15	8	-	-	69
general illness	minor		174	111	111	9	405
	major	-	21	38	25	1	85
persistent screaming		-	26	2	1	-	29
skin symptoms		-	3	42	26	4	75
discoloured legs		-	113	10	2	-	125
faints	collapse	-	144	9	5	-	158
	BHS	-	4	-	-	-	4
	fainting	-	12	-	-	-	12
fits	convulsions	-	19	35	10	1	65
	epilepsy	-	-	-	3	-	3
	atypical attacks	-	24	31	9	1	65
anaphylactic shock		-	-	-	-	-	-
encephalopathy/-itis		-	-	-	-	-	-
death		-	-	-	5	-	5
total		46	555	286	197	16	1100

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 1998.

6.9.1 Local reactions

In 1998, 69 predominant local reactions were reported in approximately equal frequencies after DPTP/Hib or DTP vaccinations. All reported local symptoms were considered reactions (table 12). 32 Children had common mild or moderate local inflammation and 22 children with mild or moderate local reactions had atypical symptoms; these included itchy rash, exanthema, pigmentation and depigmentation, scaring, local eczema, regional (?) lymphadenopathy and once possible fixed drug eruption. Some children had pain only, at the injection site, without other signs of inflammation and avoided use of the limb (completely) or limped for some time. Mostly they were moderate reactions of common inflammation, in

22 cases with atypical symptoms. Mostly the symptoms were one-sided (13 times DPTP and 5 not specified) but once definitely both sided and 13 times probably both sided.
Altogether 15 children had so called major local reactions. Six children had severe or prolonged local reactions, twice with some atypical symptoms, and all one sided. Two children with major local reactions had fever over 40.5°C. Of the nine children with abscesses the two reports about BCG could not be substantiated. Of the other seven cases none had cultures performed and all drained spontaneously; twice the abscess was definitely at the DPTP site and five times the site was not attributable to a specific vaccine. No faulty procedures were detected.
Three times the reaction was definitely at the MMR site, once MMR1 and twice MMR2. Of the other six times with simultaneous DTP five were ascribed to DTP and once the reaction site was not specified.
There was an increase in reported local reactions as compared to 1997 mainly following DPTP/Hib vaccinations, both in the numbers of minor reactions as in the number of abscesses. The number of reported abscess in previous years ranged from 0-4, but variable numbers over earlier years are reported.

Table 12. Local reactions and vaccines of reported AEFI in 1998

vaccine⇒ / event⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/hib?	mmr1	dtp5	dtp6/mmr2	bcg	total 1998	1997	1996
mild/moderate	6	4	3	4[a]	4[b]	-	6[c]	5[d]	-	32	28	20
severe/prolonged	1	-	-	3	-	-	-	2	-	6	8	7
abcess	3	2	1	1	-	-	-	-	2[e]	9	-	4
atypical moderate	2[f]	5	4	4[g]		1	2	3	1	22	13	15
total	12	11	8	12	4	1	8	10	3	69	49	46

[a] once dptp only and once dptp/hib1 catch up dose refugee
[b] twice dptp only
[c] once dtp3/hib1/mmr1 and once dtp2 in catch up schedule
[d] twice dtp only
[e] unsubstantiated rumour
[f] once with hepb1
[g] once first dptp/hib/mmr in catch up schedule

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.

general minor illness

In 405 children the complaints were considered minor illness in 1998, in 28% with no causal relation with the vaccination (28% also in 1996 and 1997) (see table 11). 79% (83% and 87% in 1996 and 1997 respectively) of reports concerned the scheduled DPTP/Hib vaccinations, most frequently events following the first DPTP/Hib (table 13). For comparison the numbers of 1994-1997 are included.

Table 13. Minor illness and vaccines of reported AEFI in 1994-1998

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

[a] twice dptp only
[b] once dptp only and once hib only
[c] once dptp only
[d] twice dptp only, twice dtp only and once dtp/hib and once opv only
[e] once mmr0 and once single measles vaccine
[f] once dptp
[g] once mmr only and once dtp only
[h] once menB trial vaccine and once tetanus single vaccine

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, 135, twice only subfebrile temperatures (37.5-<38.5°C). In all but 17 cases possibly causally related. Fever was also the most frequent symptom in the other diagnoses (112 times). Crying was the second most frequent main symptom (50), 35 times fierce and 12 times prolonged and three increased or unusually pitched; in three cases the crying had other causes. There often was pronounced crying in the other events also (41) or groaning (11). Irritability was quite frequently diagnosed (10), as were chills (13) and (sleeping) jerks or myoclonics (16), with or without fever, as often as main working diagnosis as in accompanying symptoms. Apathy or sleepiness was the main feature in 11 cases. Pallor as main or sole symptom was quite frequent as well (27), as were gastric-intestinal complaints (23). Respiratory tract symptoms like common cold, tonsillitis, pseudocroup, pneumonia, otitis, asthma, whooping cough, bronchitis etceteras, were frequently diagnosed (25). Like other years there were a few children with bulging fontanel (2), but none were considered causally related. In 1998 four children with red urine (myoglobinuria?) were reported. The case of possible whiplash resulted from a blow from an overwrought parent on the head of the child health professional; the child itself had only mild symptoms after the vaccination. See for further symptoms and causality table 14.

Table 14. Main (working) diagnosis or symptoms in minor illness of reported AEFI in 1998 (with number of assessed adverse reactions)

symptom or diagnosis	1998	(adverse reaction)	1997	(adverse reaction)	symptom or diagnosis	1998	(adverse reaction)	1997	(adverse reaction)
fever	135	(118)	70	(59)	pallor and/or cyanosis	27	(27)	26	(26)
low temperature	-	-	1	(1)	jaundice	-	-	1	(-)
crying	50	(47)	34	(31)	rash illness	25	(2)	19	(1)
irritability	10	(7)	11	(9)	vaccinitis	9	(8)	9	(9)
meningismus	1	(-)	-	(-)	parotitis	3	(2)	2	(1)
myoclonics	16	(15)	10	(10)	swelling face/hands/?	4	(2)	-	-
chills	13	(13)	6	(6)	lymphadenopathy	2	(1)	1	(-)
bulging fontanel	2	(-)	4	(1)	infectious disease	3	(-)	-	-
listlessness	1	(1)	3	(2)	allergy	1	(-)	-	(-)
drowsiness	3	(2)	2	(2)	feeding difficulty	6	(4)	2	(2)
prolonged sleep	8	(8)	3	(3)	vomiting	3	(2)	5	(3)
behavioural problem/ - illness	5	(-)	2	(-)	diarrhoea	2	(-)	-	-
neck pain/stiffness	2	(2)	-	-	gastro-enteritis	11	(4)	10	(6)
arthralgia/arthritis/coxitis	3	(2)	1	(-)	dehydration	1	(-)	-	-
lying still/frozen	10	(8)	2	(2)	myoglobinuria?	4	(4)	2	(2)
limping/falling	3	(2)	-	(-)	urinary tract infection	1	(-)	-	-
apnoea	1	(-)	-	(-)	epistaxis	1	(-)	-	-
asthma attack	2	(-)	6	(1)	whiplash	1	(1?)	-	-
airway infection	16	(-)	8	(-)	headache/migraine	2	(-)	-	-
cough	2	(-)	3	(-)	rolling eyes	1	(1)	1	(1)
dyspnea/wheezing	1	(-)	2	(-)	light sensitivity	-	-	1	(1)
pseudocroup	1	(-)	3	(-)	congenital nystagmus	1	(-)	1	(-)
tonsillitis	1	(-)	1	(-)	transient episode undefinable*	4	(1)	-	-
otitis	1	(-)	-	-	not specified	6	(2)	2	(-)

For MMR vaccinations 73 events were reported, 10 times in combination with DTP6. Of these 26 were considered possible adverse reactions, being only six times fever (of the 14 reports concerning fever), of which twice attributed to DTP, and only once crying. For DPTP vaccine (combinations) there were 313 reports, of which 121 had fever as the working diagnosis with in all but seven inferred causality. For crying there were 47 reports and in only three cases the causal relation seemed unlikely.
Altogether the rise in reported adverse reactions in MMR (combinations) was 14 cases and per DPTP dose 19.

major general illness

In 1998, 85 reports were classified as major general illness (51 and 57 in 1996 and 1997) (table 15). The distribution is more even over the scheduled vaccines than in the minor illness group. For causality see table 16. Overall 58 events were considered adverse reactions (69%) and 25 chance occurrences. One event was not classifiable.
Very high fever of ≥40.5°C was the working diagnosis in 49 cases and three times there was prolonged high fever. In the other events in this category very high fever was present in eight cases. In other event categories there was very high fever in another 36 cases, mainly in febrile convulsions.

Table 15 Major illness and vaccines of reported AEFI in 1998

diagnosis⇓ vaccine⇒	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	mmr1	dtp5	dtp6/mmr2	other	total
high fever	12	13	7	14	5	1[a]	-	-	52
arthritis	-	-	-	-	3	-	-	-	3
hemiparesis	-	-	-	-	1	1[b]	-	-	2
cerebral infarction	1[c]	-	-	-		-	-	-	1
pneumonia/bronchitis	-	-	-	-	2	-	-	-	2
rash illness	-	-	-	1	2	-	-	-	3
vaccinitis	-	-	-	-	2	-	-	-	2
sepsis	-	-	-	-	1	-	-	-	1
meningitis	2	1	-	-	-	-	-	1[d]	4
myoclonics	-	-	-	1	-	-	-	-	1
abducens paresis	-	-	-	-	-	-	1[f]	-	1
myocarditis	-	-	-	1	1	-	-	-	2
ITP	-	-	-	-	2	1[e]	-	-	3
acute cerebellar ataxia	-	-	-	-	1	-	-	-	1
psychiatric illness	-	-	1[c]	-	-	-	-	-	1
diabetes mellitus	-	-	-	-	-	-	-	1	1
kawasaki?	1	-	-	-	-	-	-	-	1
retardation	-	1	-	-	1	-	-	-	2
hypoglycaemia	-	1	-	-	-	-	-	-	1
infection	-	-	-	1	-	-	-	-	1
total	16	16	8	17	21	3	1	2	85

[a] dtp with first hib catch up dose
[b] dptp5 in child, could not be substantiated
[c] dptp only
[d] hib meningitis long after last hib vaccination
[e] mmr1 as catch up dose with dtp5
[f] dtp only

Table 16. Major illness and causal relation of reported AEFI in 1998

diagnosis⇓ causality⇒	certain	probable	possible	improbable	unclassifiable	total
high fever	-	21	27	4	-	52
arthritis	-	-	1	2	-	3
hemiparesis	-	-	1	1	-	2
cerebral infarction	-	-	-	1	-	1
pneumonia/bronchitis	-	-	-	2	-	2
rash illness	-	-	-	3	-	3
vaccinitis	-	-	2	-	-	2
sepsis	-	-	-	1	-	1
meningitis	-	-	-	4	-	4
myoclonics	-	-	1	-	-	1
abducens paresis	-	-	1	-	-	1
myocarditis	-	-	-	2	-	2
ITP	-	-	3	-	-	3
acute cerebellar ataxia	-	-	1	-	-	1
psychiatric illness	-	-	-	-	1	1
diabetes mellitus	-	-	-	1	-	1
kawasaki?	-	-	-	1	-	1
retardation	-	-	-	2	-	2
hypoglycaemia	-	-	1	-	-	1
infection	-	-	-	1	-	1
total	-	21	38	25	1	85

Of the reported events in 1998, 22 followed MMR vaccination, in all but once MMR1 single vaccine. One time MMR1 was given as catch up vaccine simultaneous with DTP5.
Six times this was very high fever, twice with a rash in the appropriate time period. In all

three children with ITP, this was considered possibly caused by the vaccine. One child suffered from post infection cerebellar ataxia and once there was a reactive arthritis, both possibly related with the MMR vaccination. One child had fever and apathy and seemed to suffer from hemiparesis with swollen hand and hyperaesthesia; no definite diagnosis could be made. This was judged possibly causally related. All children recovered completely. The other events following MMR were considered coincidental (table 15). Figures are comparable with 1997.
In 1998, 63 events followed DPTP, Hib or DTP vaccinations, with in 47 cases assessed causality (75%). This was 44 times fever, once myoclonics, once M. abducens paresis and once repeated periods of hypoglycaemia with possible underlying metabolic illness. For the other listed events the time interval was not plausible or other causes had been established; these were considered to be coincidental. The increase in reports compared to 1997 seems to be in the high fever group, with also a higher percentage causally related. The rise in reported possible adverse reactions following MMR was five and per dose DPTP seven.

6.9.3 Persistent Screaming

In 1998, 29 children with persistent screaming were reported (in 1994,1995,1996 and 1997 respectively 34, 22, 16 and 26). One child with possible persistent screaming is not included but only listed under discoloured legs. In nine cases there was also fever on the day of vaccination, twice over 40,5°C. As was noticed in former years this reported adverse event seems age/dose dependent (see table 6). Local symptoms were pronounced in 12 cases, of which five mainly had (presumed) pain at the injection site and avoided use of the legs. Some children had both sided local reactions. Additional symptoms were restlessness, feeding difficulty, swollen eyes. Parents were usually desperate and five contacted the family physician and one went to hospital where an EEG was performed. We did not record the degree of intervention in five cases, however. In all but one child (time interval with the vaccination considered too long) there was a possible or probable likelihood that the vaccination was causally related with the event.

6.9.4 General skin manifestations/phenomenon

In 1998 skin symptoms were the main or only feature in 75 reports (1996 and 1997, 58 and 74). 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 1998

vaccine⇒ / symptoms⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/hib?	mmr1	dtp5	dtp6/mmr2	hepb	total
angio-edema	-	1	-	-	-	1	-	1	-	3
vesicles	-	1	-	-	-	-	-	-	-	1
exanthema	3	5	4[a]	2[b]	-	8	2	2	1	27
erythema	1	-	-	2[c]	-	2	-	-	-	5
harliquin	1	-	-	-	-	-	-	-	-	1
urticaria	3	2	1	4	-	7	2	3	1	23
eczema	4	4	2	1	1	-	-	-	-	12
petechiae	1	-	1	-	-	1[d]	-	-	-	3
total	13	13	8	9	1	19	4	6	2	75

[a] once dptp/hib/hepb
[b] once hib only
[c] once dptp/mmr
[d] single measles vaccine

Exanthema, urticaria and (increased) eczema were the most frequent symptoms.
There were three children with petechial rash on upper body and face. Children with petechiae on the legs only are categorised under discoloured legs. 20 Cases concerned MMR1 (once a late report of single measles vaccine and once as catch up dose with in two-year-old child) with ten times (possible) causal relation. The seven times MMR was combined with DTP or DPTP the symptoms occurred on the day of the vaccination with a possible causal relation with either vaccine. This resulted in possible causal relation with MMR in 61%. The other events were not considered causally related with the vaccination. For the other vaccines or combinations, possible causal relation was assessed in 35 out of 56 events, comparable with the rate of MMR.

Table 18. Skin symptoms and causal relation of reported AEFI in 1998

causality⇒ / symptom⇓	certain	probable	possible	improbable	unclassifiable	total
angio-edema	-	-	2	1	-	3
vesicles	-	-	1	-	-	1
exanthema	-	1	16	10	-	27
erythema	-	2	2	1	-	5
harliquin	-	-	1	-	-	1
urticaria	-	-	12	11	-	23
eczema		-	7	3	2	12
petechiae	-	-	1	-	2	3
total	-	3	42	26	4	75

6.9.5 Discoloured legs

Starting from 1995, discoloured legs is 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. Descriptive epidemiology and follow up of these reports will be published separately.

In 1998 125 reports were received (1995,1996 and 1997 93, 99 and 95). Of these 24 were blue legs (18 double-sided), 56 red legs (once arms and 27 double-sided) and 30 purple legs (23 double-sided). Of the 43 one-sided discoloration eight concerned the Hib leg and 22 the DPTP leg, and in 14 cases this could not be decided. In total, 33 children had petechiae, including 14 reports without noted prior discoloration of the legs; 25 times double-sided and eight times one-sided of which twice on the Hib side, twice on the DPTP side and four times undecided; once there were also petechiae in the neck (table 19).
About 36% of the children had also fever of which four ≥40.5°C. Two thirds of the children exhibited fierce crying of whom three for several hours (twice possibly persistent screaming, once also listed in that category). Injections site reactions, if any, were not pronounced, but 16 times severe pain (twice extreme) was noted, eight times without other signs of inflammation. Six children had also collapse reaction. These compound reports are grouped under collapse also. Two children were reported with recurrent discoloured legs. Reports of discoloured legs were most frequent after the first DPTP/Hib vaccinations and decreasing in number with dose number and age.
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 1998

vaccine⇒ / symptoms⇓	dptp/hib1	dptp/hib2	dtpt/hib3	dptp/hib4	(petechiae)	total 1998	1997	1996	1995
blue legs	16	8	1	-	(5)	25	23	18	21
red legs	33	15	1	7	(6)	56	38	41	47
purple legs	12	11	7	-	(8)	30	23	27	19
petechiae only	5	7	2	-	(14)	14	11	12	6
total	66	41	11	7	(33)	125	95	98	93

Compared to 1996 and 1997 there was an increase in reports of about one quarter, predominantly after the second dose. Also we recorded a higher percentage of children with fever and fierce crying as accompanying symptoms.
Further details of this specific adverse event will be published in a separate RIVM report (descriptive epidemiology of discoloured legs 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 1998 there were 158 collapse cases (1996 and 1997 respectively 120 and 145), four times BHS and 12 fainting in older children. The four 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[32].

Table 20. Faints and vaccines of reported AEFI in 1998

vaccine⇒ event⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	mmr1	dtp5	dtp6/mmr2	total 1998	1997	1996	1995	1994
collapse	104	28	20[a]	5[b]	2	-	-	158	145	120	137	134
bhs	3	1	-	-	-	-	-	4	4	7	2	n.r
fainting	-	-	-	-	-	7	5[c]	12	6	7	8	7
total	107	29	20	5	2	7	5	174	155	134	147	141

[a] once dptp only
[b] once dptp only and once hib only
[c] once influenza vaccine only
n.r not registered (seperately)

In 1998 there were five children with recurrent collapse reported. This was somewhat more than in previous years. Some of these episodes were very incomplete and in none of the children this led to cessation of pertussis vaccinations. Five collapse cases were considered not related because of the too long time interval. 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.

Table 21. Fits and vaccines of reported AEFI in 1998

vaccine⇒ event ⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	mmr1	dtp5	other	total 1998	1997	1996	1995	1994
febrile convulsion simple	-	-	6[b]	16[c]	17	-	-	39	27	24	23	27
complex	-	-	2	8	6	1	-	17	18	8	18	20
tonic	-	-	-	2	-	-	-	2	1	3	10	n.r
atypical	1	-	2	-	-	-	-	3	6	3	7	3
non febrile convulsion	-	-	1	3	-	-	-	4	5	4	6	5
epilepsy	1	2	-	-	-	-	-	3	5	3	3	3
atypical attack	21[a]	5	16	13	9	-	1[d]	65	45	28	30	16
total	23	7	27	42	32	1	1	133	108	73	97	74

[a] three times dptp only
[b] once combined with hepb3
[c] once dptp only and once dtp/hib4
[d] influenza vaccine
n.r not registered (separately)

Most convulsions were accompanied by fever, occurring predominantly after the fourth DPTP/Hib and MMR1 vaccinations. The non-febrile convulsions are more 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 (table 22). Of the seven children with non-febrile convulsions in 1998, all followed DPTP/Hib

vaccinations. Altogether 22 children had fever of over 40.5°C, five times in children with atypical attacks and 17 times with convulsions.
In 1997 in this category there was 19 times very high fever of ≥ 40.5°C, seven in the atypical attacks and 12 in the convulsions.
The increase in reports seems to be in febrile convulsions after DPTP/Hib3 vaccination and in atypical attacks following the first and third doses. The number of atypical attacks increased already in 1997, which has lead to reviewing all cases of 1996 and 1997. For 1998 under this category there were 12 children with possible chills and six with myoclonics. Eight children turned blue, twice with possible breath holding spell, six children were hypertonic and another eight limp. In two children the attack was asymmetrical. None of the children fulfilled the case definitions for collapse or convulsion.

Table 22. Fits and fever of reported AEFI in 1998

	1998				1997			
event⇒	convulsions**		atypical attacks		convulsions*		atypical attacks	
vaccine * ⇓	<38.5°C	≥38.5°C	<38.5°C	≥38.5°C	<38.5°C	≥38.5°C	<38.5°C	≥38.5°C
dptp/hib1	1	1	12	9	2	1	7	4
dptp/hib2	2	-	2	3	1	2	5	3
dptp/hib3	1	10	8	8	-	2	2	5
dptp/hib4	3	26	3	10	1	16	4	6
dptp/hib?	-	-	-	-	-	-	1	-
dptp/hib+mmr	-	-	-	-	-	1	-	-
mmr1	-	23	4	5	5	25	-	7
dtp5	-	1	-	-		1		-
dtp6/mmr2	-	-	-	-	1	-	1	-
other	-	-	1	-				
total	7	61	30	35	10	47	20	25

* scheduled vaccines, for more specifics see table 21
** including epilepsy

See for sex distribution and causality table 10 and table 11.
In 1998 MMR was involved in 32 reports, in all instances as single vaccine, with inferred causal relation in 22. Thus there was imputed causal relation with MMR in 69% (1997 66%) and for the other vaccines in 87% (1997, 76%) of cases.

6.9.8 Encephalopathy/encephalitis

In 1998 there were no cases of encephalopathy or encephalitis reported.

6.9.9 Anaphylactic shock

No cases were reported in 1998. In matter of fact, we could never received notification of anaphylactic shock with infer 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 1998 five notifications came in of children who died after a vaccination of the RVP (table 23). There were two boys and three girls. The events were not considered to be caused or aggravated by the vaccine in all cases, nor was there undue delay in diagnosis or therapy because of the vaccination in four of the cases. In one case the information was insufficient for a definite diagnosis and no autopsy was performed. Since there were no precipitating symptoms and the child was not ill before it 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 within 24 hours of the vaccination. One report came in seven years after the vaccination on request of the parents who were concerned about a possible link of leukaemia and childhood vaccinations.

Table 23. Death and vaccines of reported AEFI in 1998

child	sex	age	vaccines	time interval		symptoms/diagnosis	causality*	autopsy
				illness	death			
A	male	7 months	dptp/hib2	birth	2 days	vitium cordis, renal insufficiency, digitalis intoxication with fatal arrhythmia	no	yes
B	female	16 months	mmr1	2 days	5 days	haemorrhagic shock encephalopathy, with cerebral edema and cerebral contusion	no	yes
C	male	16 months	mmr1	-	2 days	sids	no	yes
D	female	3 months	dptp/hib1	-	<24 hours	clinical sids	no	no
E	female	3 months	dptp1	4 weeks	6 years	leukaemia	no	?

* yes=inferred causality certain, probable or possible; no= inferred causality improbable or absent

Child A, a boy of nearly eight months of age died two days after his second DPTP/Hib vaccination. He had congenital malformation of the heart, for which he was operated when he was four months old. There were no problems on the day of vaccination but he developed fever a day later. The next day he died unexpectedly. Autopsy revealed previously unnoticed renal failure leading to digitalis intoxication with fatal arrhythmia as cause of death.
Child B was sixteen months old when she received her first MMR vaccination. Two days later she developed a common cold with coughing and very high fever for which she was given paracetamol. The next day she developed a febrile status epilepticus with extreme hyperthermia. Despite intensive treatment her condition deteriorated. The clinical diagnosis was haemorrhagic shock encephalopathy; the EEG became iso-electric on the fourth day after vaccination. She died the next day. Autopsy revealed extensive cerebral oedema with marked contusion of brainstem area.
Child C was a boy of 16 months. He was healthy at the time of MMR1 vaccination, with normal development and a weight curve below but parallel P_{10}. The night before his death he cried for some time but was quiet again before the parents decided to go and have a look. The following morning he was found dead. Autopsy revealed no cause of death; the only feature was unexplained pinpoint light resistant/refractive pupils.

Child D, a girl of nearly four months old, got her first DPTP/Hib vaccinations. Afterwards she cried more and therefore the father took her downstairs. They fell asleep on the couch. The next morning the child had died. No autopsy was performed.
Child E was a girl who had received her first DPTP vaccination when she was three months old. Four weeks later at the time of her next vaccination she became ill, first showing petechial rash and splenomegaly. Leukaemia was diagnosed. She died six years later. No further details were obtained. She was reported because the parents wondered about the relation of leukaemia and childhood vaccinations.

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 [21]. 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 24h central telephone information service 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, 1998, was followed with special attention, because of the use of a better defined pertussis component in the DPTP combination vaccine. On average this vaccine has a higher potency in the mouse protection test than before. Because of the resurgence of pertussis, with over 3500 cases a year in 1996/1997 the Inspectorate of Health Care decided to this vaccine from December 1997 onwards, with interruption of the use of prior lots. These lots were retrieved from the Child Health Clinics when supplying the new vaccine lots. We expected a rise in notifications because of possible increased attention and may be also because of possible higher reactogenicity of the vaccine.
We told Clinic Staff to maintain the usual reporting habits, with the same (wide) reporting criteria as before, and continue the registration of the lot numbers as well.

7.1 Increase in Number of Reports

There was a marked and sharp increase in notifications from December 1997 onwards with 1100 reports in 1998. This is more than could be explained by the trend, increased birth cohort or vaccination coverage.
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]. With introduction of new vaccines it is to be expected, even if they are administered simultaneously with existing vaccines, that there is a rise in true adverse reactions as well as a rise in reported events that are coincidental but regarded as possibly related with the new and yet unknown vaccines. There was levelling off of the steady increase in 1996 and 1997. In 1998 there was another step up. Reporting criteria have not been 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 have 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. This situation increases the

relative importance of potential side effects. This may influence the willingness to report possible adverse reactions as well. The change in the pertussis component of the DPTP vaccine did not go unnoticed to (potential) reporters, since the replacement of not yet expired vaccine is very much out of the ordinary. We have as yet never had to recall a vaccine either. Moreover the professionals were advised in a letter that the new vaccine worked "stronger" than the old one. Inevitably this lead to very many questions about possible "stronger" side effects as well over our telephone information service, even before the vaccine was in actual use. We told callers that we would keep the finger on the pulse as usual and asked them to keep up their regular reporting habits and criteria. Although there was a sharp increase immediately after the replacement and even before actual use of the vaccine, there was no subsequent return to levels of 1997 and before.
Below we will discuss some aspects of the reports and how these may shed light on the increase in numbers. We will not only look into the numbers of reported adverse events and relative frequencies, but also discuss some other possible signs of increased (perceived) severity or impact of the events. As there is the ratio for instance of adverse events to adverse reactions, the degree of medical intervention and the reporting interval/delay.

7.1.1 Vaccine Doses and Schedule

The distribution (relative frequency) over the different (doses of) vaccines and over the different event categories is similar to 1994-1997 (tables 5 and 6 and figures 2 and 3). Absolutely the greatest increase is in reports after DPTP/Hib of which there are four doses (54 increase per dose on average), but the relative frequency over the four doses combined stays within the range of the four previous years. There seems to be a bit of levelling between the first and second doses. Relatively the increase in reports of AE after MMR1 (increase of 42) is even larger. This may reflect some better awareness. We have in the past years stressed the importance of specific follow up after the MMR1 vaccination. The next clinic visits are quite time spaced and the need for further vaccinations is far off and both parent and clinic staff might not get to discussing events following prior MMR1 vaccination. The increase in reported AE after DTP5 and DTP6/MMR2 is relatively high, but concerns small numbers and is therefore not of much importance.
More so than in past years we have received multiple reports (26 vs 12-14 in 1996 and 1997) although small in absolute number. Since criteria for multiplicity are different for simultaneous reports as for time spaced reports this is not easy to interpret, also this may reflect differences in (timing of) follow up. It does not appear to be a consequence of relaxation of contraindications, since only very few children had conditions that might have led to deferral of vaccination in the past. The number of compound reports is similar to prior years.

7.1.2 Events, Severity and Causality

There seems to be an overall increase in numbers per category, but most pronounced in local reactions, general illness and within the fits category atypical attacks. Numbers of reported skin reactions stayed the same. This may reflect what we believe to be true: that these are coincidental anyway. The relative increase in discoloured legs and more so collapse reactions

is smaller than the overall increase also. If there were attention bias one would expect on average more coincidental events as well as a decrease in severity. Neither is the case. The percentage of adverse reactions (with causality assessed as certain, probable or possible) increased a little from 78% to 81 %. And the share of major events, by definition, with minor events with hospital care added, increased from 58% to 61%. More over the relative frequency of adverse reactions in the major group rose more than the percentage of adverse reactions in the minor group. The rise is only very small however and could be consistent with an increase in more consistent reporting and further decreased underreporting.

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 stable (4.7%). The reporting route also is very consistent over the years with the nearly all reporting by telephone. Sometimes special report forms were used for notifications and only one or two reports came in by E-mail and very few by fax.
Even paediatricians reported primarily by telephone and only one report was by discharge letter. Most of these reports came in during the acute phase of the adverse event in the need for consultation. Discharge letters carry an inherent delay, by which time most of the reports have been made by the health clinic personnel. The hospital information we received, was in majority send in following our specific request after the notification by the Child Health Clinic. In reporting route and type of reporters we cannot find an explanation for the increase in the number of reports.
Increased (perceived) severity of events and/or apprehension could lead to shorter reporting interval.
There seems to be a shorter interval between the event and notification not so much for the first two DPTP/Hib vaccine doses but for the third and fourth dose, with 32% and 39% of notifications within four weeks after the vaccination. The planned consecutive clinic visits after these vaccine doses are usually 6-8 weeks later. For comparison in 1997 with 22% and 26% reports were received within 4 weeks. For MMR1 this percentage was stable (34%). This seems to point to increased concern if not to increased severity.

7.1.4 Source of Information and Intervention

Information about the adverse event was retrieved from others than the initial reporter in 66%. More parents were contacted then the year before, not so much because of the severity of events as well as because of the 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 the public concern about possible adverse events. More parents contacted the clinic or phoned the GP than in 1997 (94 as opposed to 168) an increase in relative frequency from 11 to 15%. The proportion of children actually seen by the GP or hospital specialist remained stable (~42%), but actual numbers rose.

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). For 1993 to 1997 these rates have shown an increasing more equal

distribution. An exception was for some time the downing trend of the city of Den Haag, a long time "faithful" reporter. This year the average rate has gone up again, with as outlier the rates for Den Haag, now above average. It could well be that this is because of efforts of RIVM to get insight of this downward trend, but also just a sign of random fluctuation (regarding the small population numbers). If we regard the rates of Den Haag and compare them to the other regions, remarkable is the different distribution between minor and major events. In all the other regions this is about half minor and half major, but in Den Haag it is two-thirds over one-third for minor versus major. Averaging the three big cities, makes them lie within limits of the countries average.

7.1.6 Attention Bias and Change in Contra-indications

Attention bias could well be a reason for more reports. One would expect this to reflect in more coincidental events and in relatively more minor events. Since we rely mostly on our own diagnosis and causality assessment overrating (or underrating) the severity or dramatising (or belittling) the event will be of no consequence.
Increased attention could also result in decreased underreporting. The increase if reports following MMR, with no change in vaccine, seems to reflect this.
One reason for an increased number of adverse events could be the relaxation of contraindications. Since 1993 collapse reactions and prior convulsions are not considered contraindications anymore[25,32]. This could have some effect on subsequent adverse events. If we consider recurrent collapse reactions this does not seem to be the case, since the multiple reports on collapse seem to be only (very) incomplete episodes and the numbers do not attribute much. For convulsions the recurrent episodes do not involve prior contraindications and only a very small percentage of reported convulsions occur in children with prior convulsive disorder.

7.2 Specific Events

7.2.1 Collapse and Discoloured Legs

Especially reports on collapse reactions seem to be rather stable over the last five years, as is the distribution over the different vaccine doses. Despite the overall increase in reports total numbers were within random variation. We will have to look into reporting willingness of the vaccine providers with regard to this reaction not being a contraindication anymore. The impact on parents and on GP's and paediatricians less acquainted with this event remains considerable however. This will have to be evaluated as we follow the reports under the accelerated schedule of 1999, with start of the programme at two months of age.
For discoloured legs also the rise in reports lags a little behind the average increase. May be the reporting rate nears achievable maximum here also. We regard this event to be vasomotor like the collapse reactions discussed above. So possibly the same pathophysiolgical mechanism applies and the same predisposition. Fact is that these events sometimes coincide or follow one another. For 1996, 1997 and 1998 six, six and seven times respectively. Further study of this event is on the way.

7.2.2 Convulsions and Atypical Attacks

There seems to be an increase in (classic) febrile convulsions in the year under report, compared to 1997. This could easily be the result of random fluctuations since 1995 had about equal numbers. Criteria might have changed gradually also, as may have been the cut-off between convulsions and atypical attacks; this is not easily substantiated however. For 1997 and 1996 we have re-evaluated the criteria and coding within this category of fits just recently and this has not lead to readjustment of listing. Nonetheless this rise in the number of atypical attacks warrants further attention. It may well be a sign of increased apprehension and willingness to report, since the rise has been documented before a change in vaccines, schedules or components.
The stable number of reports of non-febrile convulsions may reflect the non-causality in the first place.

7.2.3 Local Reactions and Abscess

There seems to be some increase in local reactions especially in atypical presentations and in abscess. Some of the atypical presentations are related to other vaccines than DPTP/Hib and therefore not of consequence in evaluating the impact of the recent formula of the pertussis component. The increase in number of abscess appears to be significant but if we look to prior years numbers varied between 1-5, and this could be random fluctuation.
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.

7.2.4 Death

This year again five death were reported following vaccinations of the RVP. 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. 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.

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[33]. Just signal detection isn't enough anymore. 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.

7.3.1 Prevention of Side Effects

Side effects do occur and parents should know what to expect. Also what to do to alleviate symptoms. 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 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[25,34,35]. 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 of providing protection. In the year under report abandoned contraindications do not seem to have attributed 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 loss of protection.

7.3.3 Risk Communication

More and more in our telephone information service and in our adverse event surveillance system we are 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. Parents should also be 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 vaccination programme as well as for individual assessment. 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.

7.4 Safety Surveillance of the RVP

Safety surveillance of the vaccination programme seems to be of increasing importance. 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 are the core.

Assessing causal relation is regarded essential in monitoring the safety of the vaccination programme. Not everything happening after vaccination is caused by the vaccination of course. Only a few percent of the reports did not allow causality assessment, mostly by lack of information about time interval or symptoms. All unclassifiable events were considered minor or were just unsubstantiated rumour. Overall 78-80% of reports was considered adverse reaction, a little less than in 1994 (84%) and 1995 (81%); this may reflect decreased underreporting. 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. 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.

7.4.1 Route of reporting

We feel that the telephone service is an important tool in the safety surveillance of the RVP, both for capture of important adverse events and 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 aspect of the possibility of communication, timeliness and supplementation of data, but also it is an important tool for adherence to the programme, proper use of contraindications and vaccination in special circumstances.
It makes very efficient use of resources, may be not so much at the level of RIVM but in the broader perspective of the vaccination programme as a whole. Education of potential reporters is essential too, of course, but for the type of reports in a passive surveillance system this will not yield to 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 a 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

Verification and additional information with follow up is considered important in the monitoring of the safety of the vaccination programme. 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. 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

mostly 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. 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 the 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, contra-indications, 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[28].

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, especially in case of signals or expectations of a change in this respect. The change in RVP schedule to an earlier start from 1999 thwarted our plans for such a surveillance of DPTP/Hib vaccines. This however by itself deserves specific study of overall tolerability at a younger age. The planned MenB trial in which regular DPTP/Hib vaccines could have been (an extra) control group for monitoring adverse events has been postponed however. In 2001 we will 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). We may try to include a subgroup for the common minor events. Also datalinkage possibilities will be explored for future use within this project.

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 aspect of a good performing of the vaccination programme. 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, partly achieved in phase II and III trials in which the registered vaccines are used in the control groups, is planned in phase IV trials and as part of an EU project. The newly introduced acellular pertussis vaccine as booster in the four year old (from birth cohort 1998 onwards) will be followed actively and may serve as a pilot for the EUsafevac project. Hospital admission after any vaccine, gait disturbances and ITP after MMR1 are the outcomes studied in active design.
A 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, an adequate database system is a prerequisite for this. But also the quality of data put in must be good 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 with severe adverse events and vaccination in the media or medical press. Only then it is possible to answer questions from the public. It is stressed by them 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 for them it is not easy if at all possible 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 1998 the increase in number of reported adverse events appears to be due to both further decrease in underreporting and to increase of awareness and apprehension about potential side effects. Also detailed analysis suggests a possible increase in actual adverse reactions too, mainly events associated with fever and crying after DPTP/Hib vaccinations. This is consistent with the impression of some providers that lately they have encountered a shift in severity of the common adverse events like fever, crying and local reactions. Signals from the providers and from passive surveillance should be followed up with systematic study. We planned monitoring of the tolerability of the regular DPTP/Hib vaccine as part of a field trial with menB vaccine in which these vaccines could have been one of the study or control groups. 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.
A planned active surveillance (pilot) study as part of a European Union project, in the northern three provinces will give insight in certain more severe adverse events following vaccinations of the RVP. For the more common adverse events we will have to hook on to one of the future trials with menB, acellular pertussis vaccine components or pneumococcal conjugate vaccine and include the regular vaccines as control group for adverse events.
The regional distribution is 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. Detailed study of epidemiology, sequelae, follow up and risk factors should be performed regarding some specific adverse events. The increase in reported discoloured leg phenomenon should be studied, with retrospective analysis of previous (pre Hib) years and reassessment according to the current case definitions.
The 24h-telephone service for reporting, consultation and advice is an efficient and important tool of the enhanced passive safety surveillance system. Quality should be maintained.
The planned database system will allow further detailed aggregated analysis of the reports and will also facilitate systematic feed back to the reporters as well as data exchange with other bodies, national and international.
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 database system
- accelerated annual report of 1999 and 2000
- maintenance and evaluation of the current passive surveillance system
- report on descriptive epidemiology of discoloured legs and follow up
- exploration 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 1100 reports must be regarded in relation to a total of more than 2 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	College ter Beoordeling van Geneesmiddelen
42	LAREB
43-60	Medisch Adviseurs Entadministraties
61	Landelijke Vereninging Entadministraties
62	Landelijk Coördinatiestructuur Infectieziektenbestrijding
63	Landelijk Coördinatiecentrum Reizigersadvisering
64-69	Auteurs
94	SBD/Voorlichting en Public Relations
95	Bureau Rapportenregistratie
96	Bibliotheek RIVM
97-107	Bureau Rapportenbeheer
108-140	Reserve

Appendix 2 Vaccination programme 1998

STAATSTOEZICHT
OP DE VOLKSGEZONDHEID

Inspectie voor de Gezondheidszorg

VACCINATIEPROGRAMMA 1998

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

1998	1997	1994	1989
DKTP + Hib	DKTP + Hib + BMR	DTP	DTP + BMR

1. ZUIGELINGEN en KLEUTERS

VACCINATIESCHEMA

- DKTP (Difterie - Kinkhoest - Tetanus - Poliomyelitis)

Bij voorkeur op de leeftijd van respectievelijk 3,4 en 5 maanden wordt één DKTP-injectie gegeven.
De eerste drie vaccinaties moeten in ieder geval gegeven worden in de leeftijd van 2 maanden tot 6 maanden. Er dient minimaal een tussenperiode van 4 weken in acht te worden genomen tussen de drie vaccinaties.
De vierde DKTP-injectie wordt tenminste zes maanden na de derde DKTP-injectie gegeven.
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 gecontraïndiceerd is (zie R.J.F. Burgmeijer en D.J.A. Bolscher "Vaccinaties bij kinderen", 2e herziene druk, Van Gorcum 1995) en in plaats van DKTP, DTP wordt gegeven, dient degene die de enting verricht dit **duidelijk** te vermelden op de oproep-kaart, die naar de entadministratie wordt gezonden.

- Hib (Haemophilus influenzae type b)

Bij voorkeur op de leeftijd van respectievelijk 3,4 en 5 maanden wordt één Hib-injectie gegeven.

De eerste drie vaccinaties moeten in ieder geval gegeven worden in de leeftijd van 2 maanden tot 6 maanden. Er dient minimaal een tussenperiode van 4 weken in acht te worden genomen tussen de drie vaccinaties.
De vierde Hib-injectie wordt tenminste zes maanden na de derde Hib-injectie gegeven.
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.

Er 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 (Bof - Mazelen - Rodehond)

Op de leeftijd van veertien 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 het BMR-, DKTP- en Hib-vaccin in verschillende ledematen moeten worden toegediend.

Indien geen gebruik wordt gemaakt van de mogelijkheid om de eerder genoemde vaccinaties simultaan 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.
Het BMR-vaccin dient niet eerder dan op de leeftijd van veertien maanden te worden toegediend.

- DTP (Difterie - Tetanus - Poliomyelitis)

De in 1994 geboren kinderen worden in 1998 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", 2e herziene druk, Van Gorcum 1995).
Dosering: 1 ml INTRAMUSCULAIR.

2 SCHOOLKINDEREN

VACCINATIESCHEMA

De in 1989 geboren kinderen worden in 1998 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 1989 geboren kinderen krijgen in 1998 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	Gorechtkade 8, 9713 CA Groningen	050-3686350	050-3122733
FRIESLAND	Sixmastraat 2, 8932 PA Leeuwarden	058-2890555	058-2880286
DRENTHE	Lauwers 9, 9405 BL Assen	0592-395260	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 Coehoornstraat 2, 6811 LB Arnhem	026-4429242	026-4434999
UTRECHT	Zoutkamperschans 7, 3432 TZ Nieuwegein	030-6081376	030-6081517
NRD-HOLLAND	Zeilmakerstraat 40, 1991 JC Velserbroek	023-5382454	023-5386822
AMSTERDAM	Nieuwe Achtergracht 100, 1018 WT Amsterdam	020-5555460	020-5555360
ZD-HOLLAND	Europaweg 141, 2711 EP Zoetermeer	079-3418238	079-3315047
ROTTERDAM	Schiedamsedijk 95, 3011 EN Rotterdam	010-4339517	010-4339652
ZEELAND	Hollandiaplein 1, 4461 GT Goes	0113-249246	0113-249240
NRD-BRABANT	Bosscheweg 57, 5056 KA Berkel-Enschot	013-5384849	013-5384848
LIMBURG	Dalderhaag 13, 6136 KM Sittard	046-4529910	046-4584479

4. ALGEMEEN

4.1 ORGANISATIE.

De uitvoering van het vaccinatieprogramma word 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 terugontvangen oproepkaarten.

4.4 FINANCIERING.

De kosten van de uitvoering van het vaccinatieprogramma komen ten laste van de 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/contributie te hebben betaald.

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

4.7 Alle nadere regelingen welke met betrekking tot het vaccinatieprogramma 1998 worden getroffen, vereisen de goedkeuring van de Hoofdinspecteur voor de Gezondheidszorg.

4.8 Exemplaren van deze folder kunnen worden aangevraagd bij de Inspectie voor de Gezondheidszorg, Sir Winston Churchilllaan 362, postbus 5850, 2280 HW Rijswijk, telefoon (070) 340 59 79.

4.9 Voor vaccinaties, gegeven overeenkomstig bovengenoemd vaccinatieprogramma, doch zonder tussenkomst van de Provinciale Entadministraties, worden GEEN gratis vaccins ter beschikking gesteld, noch enige 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
3 maanden	DKTP-1 + Hib-1
4 maanden	DKTP-2 + Hib-2
5 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

Rijswijk, december 1997

De Hoofdinspecteur voor de Gezondheidszorg

J. Verhoeff.

Appendix 3 Package Insert DKTP

RIJKSINSTITUUT
VOOR VOLKSGEZONDHEID
EN MILIEU
BILTHOVEN - NEDERLAND

DIFTERIE-, KINKHOEST-, TETANUS-, POLIOMYELITISVACCIN

4000/2

Beschrijving en samenstelling
DKTP vaccin is een gecombineerd vaccin tegen difterie, kinkhoest, 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 kinkhoest component is een suspensie van hitte geïnactiveerde *Bordetella pertussis* bacteriën, stammen 134 en 509. 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	≥ 30	IE *
kinkhoestvaccin	4	IE
tetanustoxoïde	≥ 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	0,025	mg

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

Farmaceutische vorm en presentatie
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.: 030-748010
Vanaf 10 oktober 1995: 030-2748010

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

Indicatie
Actieve immunisatie van kinderen tot en met de leeftijd van 4 jaar tegen difterie, kinkhoest, tetanus en poliomyelitis.

Contra-indicaties
- bekende overgevoeligheid voor bestanddelen van dit vaccin.
- ernstige reactie na eerdere toediening van hetzelfde vaccin.
Bij DKTP vaccin vormen de volgende reacties na eerdere toediening een contra-indicatie: convulsie, collaps en encephalopathie.
Ten aanzien van de kinkhoestcomponent geldt dat kinderen die een convulsie hebben doorgemaakt of lijden aan progressieve neurologische aandoeningen, niet met DKTP vaccin worden geënt. In dat geval kan DTP vaccin worden gegeven volgens het DKTP entschema.

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 het produkt niet worden gebruikt. De kleurindicator zegt niets over overschrijding van de bewaartemperatuur.

Dosering en de wijze van gebruik
Eén dosis DKTP vaccin is 1 ml en dient intramusculair te worden gegeven. Een volledige immunisatie bestaat uit een primaire serie van drie DKTP entingen en een eerste revaccinatie. De primaire serie wordt gegeven op de leeftijd van 3, 4 en 5 maanden, met een interval van minstens één maand. De eerste revaccinatie ("DKTP-4") wordt tenminste 6 maanden na de laatste enting van de primaire serie gegeven, dus niet eerder dan op een leeftijd van 11 maanden.
Dit schema wordt in het Rijksvaccinatieprogramma toegepast.
Het geven van halve doses om de kans op bijwerkingen te verminderen is onjuist.

Ongewenste 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 kinkhoestcomponent in het vaccin aanleiding geven tot een ernstige reactie zoals collaps of convulsie. Ook treedt sporadisch een toestand van encephalopathie na DKTP vaccinatie op. Dergelijke complicaties worden waargenomen in een periode van 1 uur tot 3 dagen na enting. De meeste ernstige reacties worden binnen 12 uur gezien.
Artsen en apothekers wordt verzocht mogelijke bijwerkingen en in het bijzonder die bijwerkingen die niet in deze bijsluiter zijn genoemd, te melden aan de afdeling Klinisch Onderzoek van het Laboratorium voor Veldonderzoek Vaccins van het RIVM, tel. 030-742424. Vanaf 10 oktober 1995: 030-2742424.

Bewaring
Bewaren bij 2-8 °C; na bevriezing is het vaccin onbruikbaar.

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

Juni 1995

Appendix 4 Package Insert DTP

RIJKSINSTITUUT
VOOR VOLKSGEZONDHEID
EN MILIEU
BILTHOVEN - NEDERLAND

DIFTERIE-, TETANUS-, POLIOMYELITISVACCIN

400/1

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 afgevuld in:

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

Fabrikant en registratiehouder
RIVM, Postbus 1, 3720 BA Bilthoven
afd. verkoop SVM
Postbus 457, 3720 AL Bilthoven
Tel.: 030-748010
Vanaf 10 oktober 1995: 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. 030-742424. Vanaf 10 oktober 1995: 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.

Mei 1995

Appendix 5 Package Insert Hib

RIJKSINSTITUUT
VOOR VOLKSGEZONDHEID
EN MILIEU
BILTHOVEN - NEDERLAND

HAEMOPHILUS b CONJUGAAT (PRP-T) VACCIN

4026/3

Haemophilus influenzae type b conjugaat vaccin gevriesdroogd

Geproduceerd door Pasteur Mérieux sv - Lyon - France

Beschrijving en samenstelling
Haemophilus b conjugaat (PRP-T) vaccin is een gevriesdroogd Haemophilus influenzae type b polysaccharide - proteïne conjugaat vaccin bestaande uit gezuiverd capsulair polyribosylribitolfosfaat (PRP) met adipinezuur-dihydrazide covalent gebonden aan tetanustoxoid als dragereiwit. Het vaccin wordt geresuspendeerd met de bijgepakte reconstitutievloeistof (0,4% natriumchloride oplossing).

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

Het vaccin bevat geen adjuvantia of conserveermiddelen.

Farmaceutische vorm en presentatie
Hib (PRP-T) vaccin is een poeder voor injectievloeistof en wordt afgevuld in flesjes à 1 dosis en verpakt met 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.: 030-748010
Vanaf 10 oktober 1995: 030-2748010

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

Indicatie
Actieve immunisatie van zuigelingen - bij voorkeur vanaf de leeftijd van 3 maanden - en jonge kleuters tegen door invasieve infecties met (gekapselde) Haemophilus influenzae type b veroorzaakte ziekten zoals bacteriële meningitis, sepsis, epiglottitis, cellulitis en arthritis.
Immunisatie van gezonde kinderen ouder dan 5 jaar en van volwassenen wordt niet aanbevolen.
Immunisatie met dit vaccin geeft geen bescherming tegen virale meningitis noch tegen infecties veroorzaakt door meningococcen of pneumococcen.

Contra-indicaties
- overgevoeligheid voor een vaccincomponent, in het bijzonder voor tetanuseiwit
- ernstige reactie na eerdere vaccinatie met hetzelfde vaccin.

Speciale waarschuwingen en voorzorgen bij gebruik
Haemophilus b conjugaat (PRP-T) vaccin beschermt niet tegen infecties veroorzaakt door andere serotypes van Haemophilus influenzae dan serotype b, noch tegen meningitis van andere oorsprong.
Geadviseerd wordt de toediening van Hib (PRP-T) vaccin uit te stellen bij koorts of een infectie.
In geen enkel geval kan het tetanuseiwit van het vaccin de gewone tetanus-vaccinatie vervangen.

Dosering en de wijze van gebruik
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 produkt voorzichtig om te zwenken ontstaat een heldere, kleurloze oplossing.
Eén dosis bestaat uit 0,5 ml vaccin, ongeacht de leeftijd. Het vaccin dient intramusculair te worden toegediend. Niet intraveneus spuiten.

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 3 maanden) met de immunisatie aangevangen te worden.

- wanneer de eerste vaccinatie wordt gegeven vóór de leeftijd van 6 maanden: 3 primaire injecties, toegediend met intervallen van 1 maand, gevolgd door een booster op de leeftijd van 11-12 maanden.
- wanneer de eerste vaccinatie wordt gegeven op een leeftijd van tussen 6 en 12 maanden: 2 primaire injecties, toegediend met een interval van 1 tot 2 maanden, gevolgd door een booster op de leeftijd van 14-18 maanden.
- wanneer de eerste vaccinatie wordt gegeven na de leeftijd van 12 maanden: 1 enkele injectie, géén booster.

Het is nog niet bekend of het schema van 3 injecties en één herinenting verenigbaar is met het DKTP entschema volgens het Rijksvaccinatieprogramma. Daarom dient voorlopig een periode van tenminste 14 dagen in acht te worden genomen tussen de vaccinatie met DKTP vaccin en het Haemophilus b conjugaat vaccin.

Ongewenste bijwerkingen
Milde locale reacties zoals pijn, erytheem en induratie kunnen voorkomen evenals koorts. Tijdens klinisch onderzoek zijn geen ernstige systemische bijwerkingen geconstateerd.
Artsen wordt verzocht mogelijke bijwerkingen te melden aan de afdeling Klinisch Onderzoek van het Laboratorium voor Veldonderzoek Vaccins van het RIVM, tel.nr.: 030-742424. Vanaf 10 oktober 1995: 030-2742424.

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

Juni 1995

Appendix 6 Package Insert BMR

RIJKSINSTITUUT
VOOR VOLKSGEZONDHEID
EN MILIEU
BILTHOVEN - NEDERLAND

BOF-, MAZELEN-, RUBELLAVACCIN

4002/3

levend, gevriesdroogd

Licentie van Merck & Co., Inc. Rahway, N.J., U.S.A.

Beschrijving en samenstelling

Bof-, mazelen-, rubellavaccin (BMR) is een gevriesdroogd preparaat van levend verzwakt bofvirus, gekweekt op kippe-embryofibroblasten, stam Jeryl Lynn; levend verzwakt mazelenvirus, gekweekt op kippe-embryofibroblasten, stam Moraten, verkregen door de reeds verzwakte Edmonston stam door herhaalde passage in celculturen verder te verzwakken, en levend verzwakt rubellavirus, stam Wistar RA27/3, gekweekt op menselijke diploïde 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.: 030-748010
Vanaf 10 oktober 1995: 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.

Contra-indicaties

- BMR vaccin bevat levende verzwakte virusstammen en toepassing is dan ook gecontraïndiceerd bij patiënten die met corticosteroïden of cytostatica worden behandeld en bij patiënten met stoornissen in het afweermechanisme, met uitzondering van HIV-infecties.
- BMR vaccin is eveneens gecontraïndiceerd bij zwangerschap.

Speciale waarschuwingen en voorzorgen bij gebruik

- Bof- en mazelenvirus worden gekweekt in cellen afkomstig van kippe-embryo's.
  Overgevoeligheid voor kippe-eiwit is geen contraïndicatie; bij patiënten met anafylactoïde reacties op kippe-eiwit dient BMR vaccinatie echter onder strikte medische begeleiding te worden uitgevoerd.
- Voor gelijktijdig toedienen van vaccins zie onder dosering en de wijze van gebruik.
- Contraceptieve maatregelen moeten worden genomen tot 3 maanden na vaccinatie van vruchtbare vrouwen.
- Aanbevolen wordt vaccinatie tegen BMR minstens 3 maanden uit te stellen na transfusie met totaal bloed of plasma en na toediening van immunoglobuline afkomstig van de mens.

Dosering en de wijze van gebruik
Gebruik voor resuspensie uitsluitend de bijgeleverde reconstitutievloeistof, omdat deze vrij is van conservantia of andere virusinactiverende middelen. Resuspensie geschiedt door 6 ml (multidoses) of 0,6 ml (monodosis) van de reconstitutievloeistof met een steriele spuit bij het gedroogde vaccin te voegen. Omdat het flesje met vaccin onder vacuum gesloten is, zal na het aanprikken de reconstitutievloeistof met kracht in het flesje gezogen worden. Hierdoor ontstaat schuimvorming die echter na ca. 10 seconden verdwijnt. Het volledig geresuspendeerde vaccin is helder en oranje-geel van kleur. Eén dosis is 0,5 ml en dient subcutaan te worden gegeven. Het vaccin moet langzaam worden toegediend, bij voorkeur in de bovenarm. Niet intraveneus spuiten.

Het Rijksvaccinatieprogramma voorziet in vaccinatie op een leeftijd van 14 maanden en een tweede vaccinatie op circa 9-jarige leeftijd.
De vaccinaties kunnen in dezelfde zitting gegeven worden met andere vaccins die in het Rijksvaccinatieprogramma worden toegepast, uiteraard op een andere injectieplaats.
Als hiervan geen gebruik wordt gemaakt, dient een tussentijd te worden aangehouden van tenminste 2 weken indien het D(K)TP en/of Hib vaccin *vóór* de BMR vaccinatie is gegeven, en van 4 weken indien het D(K)TP en/of Hib vaccin *na* de BMR vaccinatie wordt gegeven.
Ook volwassenen kunnen met BMR vaccin worden geïmmuniseerd.

Ongewenste bijwerkingen
Vaccinatie kan gedurende korte tijd een 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. 030-742424. Vanaf 10 oktober 1995: 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.

Mei 1995