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RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEU
NATIONAL INSTITUTE OF PUBLIC HEALTH AND THE ENVIRONMENT

RIVM report 000001 003

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

Numbers III - IV - Reports in 1996 and 1997

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May 2001

This investigation has been performed by order and for the account of Inspectorate of Health Care, within the framework of project V/000001/01/AD Registration, Evaluation and Reporting of Adverse Events following Immunisations.

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Abstract

Adverse events following immunisation (AEFI) in the National Vaccination Programme of the Netherlands (RVP) have been monitored through an enhanced passive surveillance system by RIVM since 1962. From 1984 onwards evaluation is done in close collaboration with the National Health Council. Reports from Health Care workers are received mainly by telephone through the operating vaccine information and advisory service. Further data are obtained, if necessary, from parents, general practitioners, paediatricians etc. After supplementation and verification of data a (working) diagnosis is made and causality assessed. In this report on 1996 and 1997 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 per year 732 and 822 AEFI were submitted in 1996 and 1997 respectively. Of these 1,6% (12) and 2% (17) were unclassifiable because of missing information. In 78% (565) and 80% (642) of the classifiable events a possible causal relation with vaccination was established and in 22% (155) and 20% (163) the events were judged to be coincidental. Compared to 1995 the number of reports stabilised, with similar distribution and causality.

Acknowledgements

We are indebted to the clinic staff and other reporters of adverse events, and to all other people willing to share information, especially the parents of children with an adverse event following vaccinations.

Abbreviations

AE	Adverse Event (melding of postvaccinale gebeurtenis)
AEFI	Adverse Event Following Immunisation
AR	Adverse Reaction (bijwerking)
BCG	Bacille Calmette Guérin (vaccine)
BHS	Breath Holding Spell
CB	Child Health Clinic (consultatiebureau)
CBS	Statistics Netherlands
CIE	Centre for Infectious diseases Epidemiology (of RIVM)
DM	Diabetes Mellitus
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 Thrombocytopenic 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.
94-96% Van de spontane meldingen komen telefonisch binnen, in hoofdzaak vanuit de Jeugdgezondheidszorg. Nadere gegevens worden van ouders, huisarts of ziekenhuis verkregen in meer dan de helft van de meldingen. Na aanvulling en verificatie volgt het stellen van een (werk)diagnose en causaliteitbeoordeling door artsen van het RIVM. De beoordeling wordt meestal (en toenemend) telefonisch teruggerapporteerd naar de melder (81% en 91%). Schriftelijk verslag, veelal van de ernstiger of gecompliceerdere beelden, wordt naar alle medisch betrokkenen gestuurd.
Een speciale commissie van de GR herbeoordeelt door hen geselecteerde meldingen individueel en de geaggregeerde gegevens van het jaarrapport steekproefsgewijs tijdens een jaarlijks werkbezoek aan het RIVM. De GR adviseert de Minister van Volksgezondheid jaarlijks over de veiligheid van het RVP. Het RIVM jaarrapport bevat alle binnengekomen meldingen in een kalenderjaar.
Dit is het derde jaarrapport, waarin dit keer twee jaargangen zijn opgenomen.
In 1996 en 1997 zijn respectievelijk 732 en 822 meldingen binnengekomen, betreffende 786 en 801 kinderen op een totaal van meer dan 2 miljoen vaccinaties per jaar. Hiervan was respectievelijk 1.6% (12) en 2% (17) niet te beoordelen wegens het ontbreken van informatie.
In 1996 werd 78% (565) van de meldingen als bijwerking beoordeeld met een mogelijk, waarschijnlijk of zeker causaal verband. Over 1997 was dat 80% (642). Een toevallige samenloop werd aangenomen in respectievelijk 22% (155) en 20% (163) van de meldingen.
In 1996 werden 338 meldingen betreffende milde of matig ernstige algemene of lokale (minor) verschijnselen geregistreerd (46% van het totaal aantal meldingen). Hiervan werd 70% (238) als (mogelijke) bijwerking uitgeboekt. In 1997 waren er 368 meldingen van "minor" postvaccinale verschijnselen (45%) waarvan 83% (385) (mogelijke) bijwerking.
Ernstiger postvaccinale gebeurtenissen (gerubriceerd onder convulsies, collaps, persistent screaming en "ziek major" en enkele lokale of huidverschijnselen) werden 394 en 454 keer gemeld in 1996 en 1997. Hiervan werd 83% (327 en 385 respectievelijk) beoordeeld als mogelijke bijwerking. In geen van de gemelde sterfgevallen, negen en drie respectievelijk, werd na beoordeling een causaal verband vastgesteld. In alle gevallen werd geconcludeerd dat het ging om een toevallige samenloop, hoewel eenmaal geen diagnose kon worden gesteld.
Er waren in 1996 tien heftige lokale reacties, waarvan vier abcessen. In 1997 zijn geen abcessen gemeld en acht anderszins heftiger lokale reacties. Daarnaast was er in 1997 een huidbeeld dat als "major" werd uitgeboekt vanwege de hoge koorts.

Verkleurde benen (sinds 1995 voor het eerst afgesplitst van de huidverschijnselen) werden 99 keer gemeld in 1996 en 95 keer in 1997, met in 98 en 89 gevallen een mogelijke causale relatie. Collaps, waaronder ook atypische en onvolledige episodes, werd 120 en 145 maal gediagnostiseerd, met in respectievelijk 7 en 4 gevallen geen oorzakelijk verband. Daarnaast enkele keren breath holding spells (6 en 4) en flauwvallen (6 en 6) in oudere kinderen. In 1996 en 1997 werden 42 en 58 convulsies gemeld, waarvan 38 en 54 febriel; in 30 en 43 gevallen met een mogelijk causaal verband. De 28 atypische aanvallen (50% met koorts) hadden in 75% een (mogelijk) causaal verband in 1996; in 1997 waren er 45 atypische aanvallen (56% met koorts) en daarvan 76% als mogelijke bijwerking werd uitgeboekt. Epilepsie (3 en 5 meldingen respectievelijk) werd niet als bijwerking beoordeeld, maar als een coincidentie. Alle meldingen van persistent screaming (16 en 26) werden gezien als bijwerking. Koorts van $\geq$40.5°C was de werkdiagnose bij 22 kinderen uit de “ziek major” groep in beide jaren, met in 1996 82% en in 1997 86% als (mogelijke) bijwerking beoordeeld. Van de 29 andere beelden uit de “ziek major” groep in 1996, was er zeven keer een mogelijk causaal verband. Het ging hierbij om vaccinitis (1), rillingen (2), myoclonieën (1), alle met hoge koorts, dehydratie (1) en ITP (1). Van een kind met een oude retinitis kon een causale relatie met de eerder BMR vaccinatie niet worden uitgesloten omdat zij later een immuunstoornis bleek te hebben. De overige 22 beelden werden als coïncidenteel beoordeeld, inclusief de drie niet te achterhalen geruchten. In 1997 waren er naast de extreem hoge koorts nog 35 andere meldingen in de "ziek major" groep, met in 13 gevallen een (mogelijke) causale relatie. Eenmaal was dit pyomyositis met positieve bloedkweek op staphylococcen en driemaal ITP. Daarnaast vaccinitis(4), huilen(2), geprikkeldheid(1), diarree(1), myoclonieën(1), alle met hoge koorts. In de andere 22 gevallen waren de postvaccinale verschijnselen in 1997 gezien als coïncidentele gebeurtenissen.
Zoals in eerdere jaren gingen de meeste meldingen over DKTP/Hib vaccinaties. BMR vaccinatie was betrokken in 99 meldingen in 1996 waarvan 18 keer in combinatie met andere vaccins; in 42% (42) werd besloten tot een mogelijk causale verband. In 1997 betroffen 122 meldingen (ook) BMR, 23 keer gecombineerd, met 58% (69) als mogelijke bijwerking van BMR beoordeeld. Van de andere vaccin(combinatie)s dan BMR was er in 86% en 79% een mogelijke causale relatie in respectievelijk 1996 en 1997.
Ten opzichte van 1995 stabiliseerde zich het aantal meldingen, met vergelijkbare distributie en causaliteit.

Summary

Adverse Events Following Immunisations (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. 94-96% Of reports came in by telephone. Parents, GP's and/or hospital provide additional data on request in over half of the cases. After supplementation and verification of data RIVM makes a (working) diagnosis and assesses causality. The assessment is communicated to the reporting party usually and increasingly by telephone (81% and 91%). 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 third annual report, with AEFI over two years.

In 1996, on a total of over 2 million vaccinations, 732 AEFI were submitted, concerning 786 children. Of these only 1.6% (12) were not classifiable because of missing information. 78% (565) of classifiable events were judged to be possibly, probably or definitely causally related with the vaccination and 22% (155) of the events were considered coincidental. Minor local or systemic symptoms were registered in 338 cases of which 238 (70%) were classified as (possible) adverse reactions.

Major adverse events occurred in 394 cases (collapse, convulsions, atypical attacks, persistent screaming, general major illness and some local reactions) of which 83% (327) considered a possible adverse reaction. All nine death cases were judged to be chance occurrences although once a definite diagnosis could not be made.

There were 10 major local reactions four of which abscesses. Discoloured legs were reported 99 times with a causal relation more or less likely in all but one. The 134 reports in the faints category (in majority collapse reactions) were considered causally related 127 times, including seven breath holding spells and eight syncope in older children. Convulsions were diagnosed in 42 cases, 38 of which were febrile, with in 30 inferred causality. Atypical attacks (50% with fever) were diagnosed 28 times, of which 75% with a possible causal relation. Epilepsy (3) was not considered causally related with the vaccinations. All 16 cases of persistent screaming were considered to be adverse reactions.

High fever $\geq$40.5°C was the working diagnosis in 22 cases of the major illness group, 82% with inferred causality. Of the other 29 major illness cases in seven possible causal relation was assessed. These concerned vaccinitis (1), chills (2), myoclonics (1), all with high fever, and ITP (1) and dehydration (1); in the child with late diagnosed retinitis causal relation with the prior MMR1 could not be ruled out, since she appeared to be immuno-compromised. The other 22 AEFI were considered to be unrelated, including the three unsubstantiated rumours.

Most frequently reports involved DPTP and Hib vaccinations. MMR was involved 99 times, 18 times with simultaneous other vaccines; in 42% (42) of cases there was a possible causal relation with MMR. For the other vaccines or combinations this percentage was 81%.
In 1997, again on a total of over 2 million vaccinations, 822 AEFI were submitted, concerning 801 children. Of these 2% (17) were not classifiable because of missing information. 80% (642) of classifiable events were possibly, probably or definitely causally related with the vaccination and 20% (163) of the events were judged to be coincidental.
Minor local or systemic symptoms were registered in 368 cases of which 257 (70%) were classified as (possible) adverse reactions.
Major adverse events occurred in 454 cases (collapse reactions, convulsions, atypical attacks, persistent screaming, general major illness, and some local or skin reactions) of which 83% (385) assessed as (possible) adverse reaction. All three death cases were considered chance occurrences. There were eight major local reactions with no abscesses were reported this year. Once skin reaction was classified as major because of accompanying high fever.
Discoloured legs were reported 95 times with a causal relation 89 times. The 155 reports in the faints category were mainly collapse reactions and included four breath holding spells and six syncope in older children; 151 AEFI were considered causally related. Convulsions were diagnosed in 58 cases, 54 of which were febrile, with in 43 inferred causality. Atypical attacks (56% with fever) were diagnosed 45 times, of which 76% with a possible causal relation. Epilepsy (5) was not considered causally related with the vaccinations. All 26 cases of persistent screaming were considered to be adverse reactions.
High fever $\geq$40.5°C was the working diagnosis in 22 cases of the major illness group, with in 86% inferred causality. Of the other 35 major illness cases in 13 possible causal relation was assessed. These AEFI were vaccinitis(4), excessive crying(2), irritability(1), diarrhoea(1), myoclonics(1), all with high fever, and pyomyositis+sepsis(1) and ITP(3). The other 25 AEFI were considered to be unrelated.
Most frequently reports involved DPTP and Hib vaccinations. MMR was involved 122 times, 23 times with simultaneous other vaccines; in 58% (69) of cases there was a possible causal relation with MMR. For the other vaccines or combinations this percentage was 79%.
Compared to 1995 the number of reports stabilised, with similar distribution and causality.

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. These GR reports bear no reference to year of vaccination or adverse event nor to year of notification but only to year of reassessment by GR; therefore 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 combined 1996/1997 report, like 1995, contains a description of the procedures for soliciting notifications, verification of symptoms, diagnosis according to case definitions, and causality assessment. We will discuss some specific adverse events and their relation to the vaccination. Special attention will be given to underreporting and to prevention of adverse events and contra-indications. This RIVM report on adverse events is only issued in English. It includes a detailed description of the background, organisation and procedures of the National Vaccination Programme and the embedding in the Child Health Care System (JGZ).

2. Post Marketing Surveillance

Post marketing surveillance (PMS) consists of all actions towards better knowledge and understanding of (adverse) effects of vaccines beyond the pre-registration research. This is particularly relevant for the identification of rare as well as late adverse reactions, as their rate of occurrence can only be estimated after vaccine use in large populations over a long time [1]. Insight in overdose consequences or use in special groups or circumstances or interactions can be gained only through PMS [1]. 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. The surveillance of the RVP is a task of the National Institute of Public Health and Environment (RIVM). The safety surveillance is done by the Laboratory for Clinical Vaccine Research (LVO), and the surveillance of the effectiveness by 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 events as part of the global drug- monitoring programme [6].

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.

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. Since the GR reports have no direct reference to year of notification or vaccination and contain only 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. We hope they 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.

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 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 [10]. At first mono-vaccines against diphtheria, tetanus and pertussis were used and the combined DTP vaccine since 1957. After the polio epidemic of 1956, vaccination against poliomyelitis was added. There has been an intensive catch-up programme for all post World War II birth cohorts. From 1961 on the supply of nationally produced inactivated polio vaccine (IPV) was sufficient to meet the demands. 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. In contrast to all earlier vaccines no catch up schedule was provided for, and a country-wide public information programme to advise parents on the benefit of vaccination of all children up to 5 years of age was not undertaken. The actual RVP of 1996/1997 is included in Box 1 (Appendix 2).

Box 1. Schedule of the National Vaccination Programme of the Netherlands in 1996/1997

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 those children with higher chance 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 [10]. Hepatitis B vaccination (HepB) is available for children of HBsAg positive mothers. These vaccinations are 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. 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 [10].

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) [10]. The PEA are responsible for further distribution to the providers. They also have 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 [10].
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 used for reimbursement of the costs of vaccinating (approx. 5 Euro per vaccine). 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.

3.3 Child Health Care System

The Child Health Care system (JGZ) aims at enrolling 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 [11]. Up till 4 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 visits approximately two weeks after birth, parents get information individually 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 is 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 National Vaccination Programme 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 administering the next dose. The four-year booster shot with DTP is usually given at the last CB visit, before school entrance. Booster vaccinations with DTP and MMR at nine years of age are 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 vaccinations 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% [12].

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 [10]. 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. 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. These written assessments include the more serious reported events. Criteria for selection of the cases to be presented to GR have been mutually accepted. The other reports are crosschecked sample wise by GR. Since 1994, for reasons specified in Chapter 2, LVO-RIVM makes an annual report on adverse events and no longer indirectly via reports by GR. For further details see Paragraph 5.7.

4. Materials

4.1 Post Vaccination Events

Events following immunisations do not necessarily have a causal relation with the vaccination and some have a temporal association only and are in fact mere coincidental.[8,13] 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-biological product meant for active immunisation against one or more diseases.
- Vaccination or inoculation: all activities necessary for vaccine administration.
- Post vaccination event or Adverse Event Following Immunisation (AEFI): neutral term for unwanted, undesirable, unfavourable or adverse symptoms within certain time limits after vaccination without a presumed causal relation.
- Side effects or adverse reaction: an adverse event with a presumed or 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).[14]

Box 3. Origin / Subdivision of adverse events by mechanism

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

4.2 Notifications

All incoming information on adverse events following immunisations (AEFI) under RVP, whether reports or requests for consultation about cases are regarded as notifications. All notifications are recorded on an individual level. For notifying and information a 24-hr telephone service is available. This permanent availability with instant consultation and

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

Box 4. Subdivision of notifications of adverse events

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

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

5. Methods

5.1 Analysis

The processing and evaluation of notifications of adverse events is directed by a standard operating procedure (SOP 12 N-GCP-08). A physician reviews every incoming notification. The data are verified and the need for additional information is determined. A (working) diagnosis is made on the basis of the signs and symptoms, with assessment of the severity, duration and time interval. Causality is assessed on the basis of the type of vaccine, time interval and presumed pathophysiological mechanism of symptoms and alternative or other plausible causes of the event. The reporting person 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 care, immunology, etiology and differential diagnoses in paediatrics. The nature of the vaccine and its constituents determine which side effects it may have and after how much time. 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).

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

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 a 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 causes 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 causality assessment

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 last year, for the purpose of aggregated analysis. Formerly these events were either classified under skin symptoms or under local reactions (see also Box 7).

- 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 gastro-intestinal symptoms, crying, irritability, changed 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. Prolonged mild or moderate fever is considered minor illness.
- Persistent screaming: (sudden) screaming or fierce crying, 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 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 petechiae, with or without swelling. Extensive local reactions are not included.
- Collapse or Faints: a sudden loss of consciousness, loss of muscle tone and pallor, unless it is 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 the category collapse. Just pallor or apathy or prolonged sleeping or limpness is not considered collapse reactions.

- Convulsions or Fits: all episodes with tonic and/or clonic muscle spasms and loss of consciousness. There is discrimination by body temperature in nonfebrile and febrile convulsions: if fever is over 38.5°C it is booked as febrile convulsion unless the convulsion is symptomatic for meningitis or for other major 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. Unspecifiable atypical attacks are a separate group under fits. These are paroxysmal occurrences without the specific criteria for collapse or convulsions. Nocturnal myoclonics is 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 (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 subdivisions according to severity

local reaction	minor major	mild or moderate injection site inflammation severe or prolonged local symptoms or abscess
general illness	minor major	mild or moderate general illness not included in the other specific categories 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 major	skin symptoms not attributable to systemic disease or local reaction 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
collapse or faints		spells with pallor or cyanosis, limpness and loss of consciousness; included are also fainting and breath holding spells.
convulsions or 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 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 notifications without formal written assessment by LVO-RIVM, the final judgement on the safety of the programme is reached. Two 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. Numbers should thus not be added up.
Because the workload of the committee had to be diminished 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 years under report (1996/1997) 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 1996 all reported events have been recoded in one run by one of us (PEVdB), because the special code forms are only in use from mid 1997. For 1997 all coding have been re-appraised later. Grouped events were checked for maximum consistency. Final diagnosis, causality and categorisation have been checked sample wise by independent review of other physicians/investigators. Results were compared and showed remarkable consistency with virtually no inter-observer variability. Case definitions and cut-offs have been under discussion in the course of training of new physicians. 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 implemented.

5.9 Quality Assurance

Assessment of adverse events is directed by a standard operating procedure (12N-GCP-08). There has been an independent external inspection and the GR audit over the year 1996/1997. This will be commented upon in the combined GR report over 1996-1999.

6. Results

6.1 Number of Reports

In 1996 and 1997 LVO-RIVM received 723 and 815 notifications of adverse events on a total of over 2 million vaccinations in each year (birth cohort 189.521 and 192.443 CBS per 01-01-2000). The notifications involved 711 and 801 children because there were 12 and 14 children with multiple reports, concerning two different vaccination dates; one child had reported AE after three vaccination dates in 1996. Ten and seven reports were compound with two distinct adverse events concerning one vaccination date in the years under report. 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 RIVM report contains 732 and 822 reported AEFI.

Table 1. Types of reports in notified AEFI in 1996 and 1997

	1996		1997	
	children	adverse events	children	adverse events
single	689	688[a]	780	780[b]
multiple	12	25[c]	14	28
compound	10[d]	19[c]	7	14
total	711	732	801	822

[a] six times multiple reports in different calendar year
[b] ten times multiple reports in previous or following years
[c] once multiple and compound reports of the same child
[d] one compound report with the first event in previous year

Comparison of notifications with prior years is hampered, because only from 1994 onwards all incoming notifications are recorded in the logbook and get a file number according to year of notification. Before, only the more severe or particular events with formal written assessment were archived according to year of vaccination. The other reports were just put in store without listing.

Even without exact counts of former years, it is clear that the number of reported events rises (Table 2). This increase seems to be levelling off in 1996 and 1997. As in 1994 and 1995 the notification rate is not even over the months, range 35-72 and 59-89 with the lowest rate in winter.
Criteria for formal written assessment changed in 1996; this has had influence on the years of report, with less written assessments. See Paragraph 6.5.

Table 2. Number of AEFI per year

	written assessments[a]	total[b]
1984	91	310
1985	139	325
1986	197	350
1987	149	325
1988	143	390
1989	141	440
1990	128	375
1991	136	340
1992	147	440
1993	227	496
1994	276	712
1995	234	800
1996	141	732
1997	76	822

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

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 (3.3%) and 51 (6.2%) notifications came by regular mail in 1996 and 1997 respectively, most frequently as (hospital discharge) letter, and some on regionally used, special report forms.
Reports from Child Health Clinics accounted for about 80% 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 1996 and 1997

		1993	1994	1995	1996	tel.	mail	1997	tel.	mail
Clinic staff	Physician	341	474	548	466	454	12	547	519	28
	Nurse	40	78	102	116	114	2	142	137	5
Paediatrician		54	60	59	56	50	6	39	30	9
General Practitioner		27	25	13	26	23	3	20	19	1
School Health Service		23	15	18	15	15	-	10	10	-
District Consultant		-	9	18	11	11	-	16	14	2
Parent		11	25	34	35	33	2	40	37	3
Other		-	5	6	4	4	-	7	4	3
Unknown		-	21	2	3	3	-	1	1	-
Total		496[a]	712	800	732	707	25	822	771	51

[a] estimate

The parents of 35 and 40 children reported directly themselves; mostly they were advised to do so by the clinic staff. This percentage of parent reports seems to be rising over the last 4 years from 3.5% to 4.9%. Pharmacists reported only twice in 1996 and 3 times in 1997 with

three notifications through LAREB and another two from homeopaths. On 3 and 1 of the registration forms the reporter was not noted.

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 three regions differ significantly from the country's average of 4.2/1000 (1995) for both years under report. This does not have very much impact in absolute numbers, since these areas do not have large populations per region. Compared to 1993 and 1994 and prior the distribution of the reporting rates over the country is more even since 1995. See Table 4 and Figure 1.

Table 4. Regional distribution of reported AEFI in 1993-1997, per 1000 vaccinated infants

	1993	1994	1995	1996	95% c.i. [a]	1997[d]	95% c.i. [a]
Groningen	3.2	3.1	4.3	3.5	2.0-4.9	2.8	1.5-4.1
Friesland	1.2	2.5	4.7	3.6	2.2-5.0	4.7	3.1-6.2
Drenthe	1.1	1.8	2.0	3.2	1.7-4.7	2.7	1.3-4.1
Overijssel	1.9	2.1	4.0	2.7	1.8-3.5	4.1	3.0-5.2
Flevoland	0.5	1.4	3.4	2.6	1.2-4.1	2.6	1.2-4.1
Gelderland	1.6	2.9	4.0	3.5	2.7-4.3	3.9	3.1-4.7
Utrecht	3.5	4.6	4.2	4.4	3.3-5.5	5.0	3.8-6.2
Noord-Holland[b]	1.7	2.4	3.8	3.9	3.1-4.7	4.3	3.4-5.2
Amsterdam	4.7	8.2	6.0	4.4	2.9-5.8	6.1	4.4-7.8
Zuid-Holland[b]	3.3	4.6	5.0	4.5	3.7-5.2	4.6	3.8-5.3
Rotterdam	3.6	4.1	5.4	3.1	1.7-4.5	4.5	2.9-6.1
Den Haag	7.0	6.0	3.0	7.3	4.8-9.7	6.6	4.3-9.0
Zeeland	0.5	1.2	2.5	2.2	0.8-3.6	2.9	1.3-4.5
Noord-Brabant	2.4	3.3	3.7	4.3	3.5-5.0	4.2	3.4-4.9
Limburg	1.5	3.4	4.2	3.4	2.3-4.4	5.3	4.0-6.6
Netherlands [c]	2.6	3.6	4.2	3.9	3.6-4.2	4.4	4.1-4.7
range	0.5-7.0	1.2-8.2	2.0-6.0	2.2-7.3		2.6-6.6	

[a] proportionate confidence interval
[b] provinces without the three big cities Amsterdam, Rotterdam, Den Haag
[c] the Netherlands have a birth cohort of approximately 191.000 per year and coverage of 97% on average
[d] coverage data of 1996 have been used for the rates, because IGZ data of 1997 have not yet become available

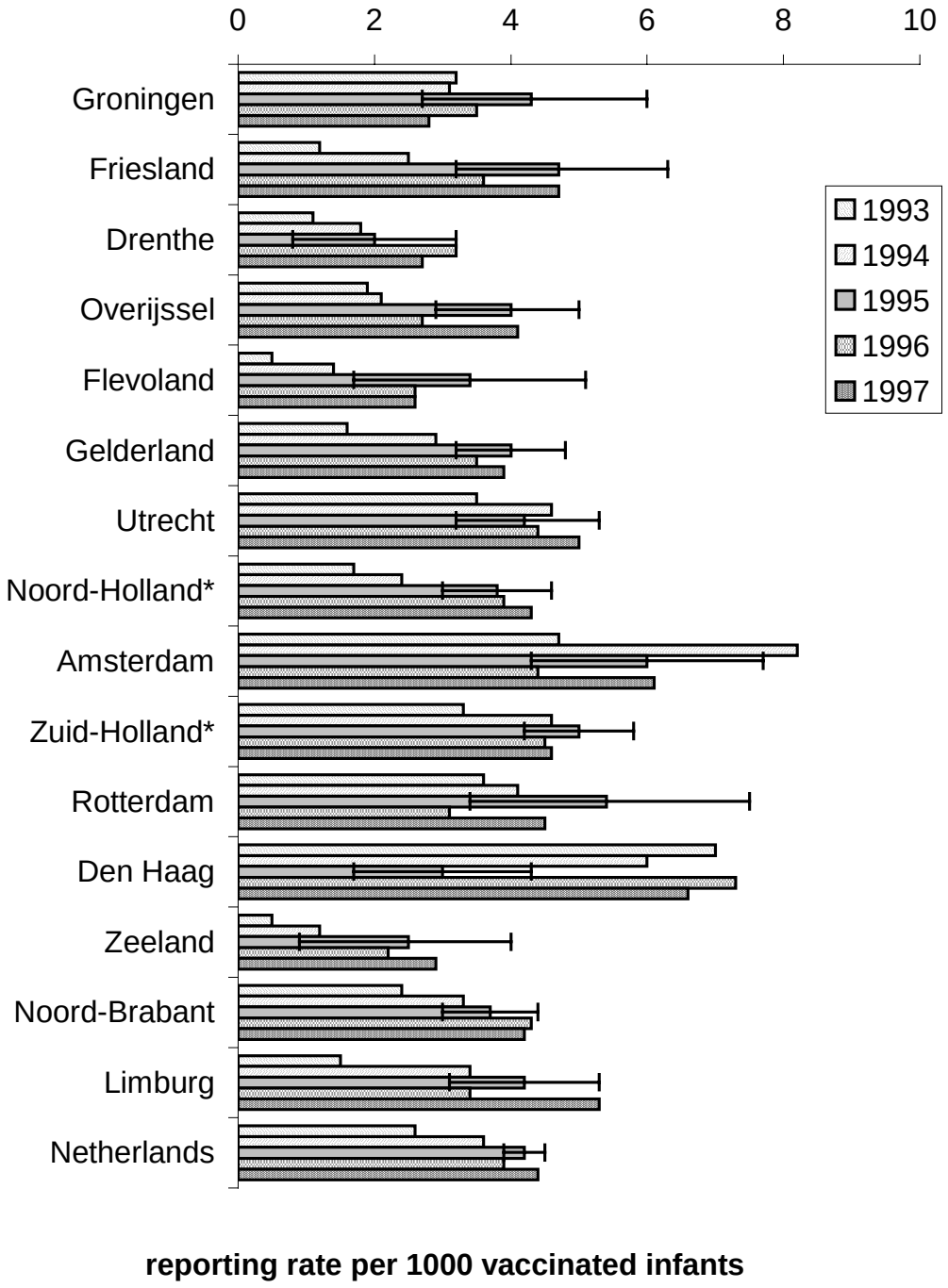

Figure 1. Number of reported AEFI in 1996 and 1997 per 1000 vaccinated infants

6.4 Vaccines

In 1996 and 1997, most notifications were about recent vaccinations, all except 20 and 21 respectively. These latter notifications arose from concerns about planned booster vaccination or vaccination of younger siblings. As in prior years, reports on the first simultaneous DPTP and Hib vaccinations were the most prevalent (284 and 323), with declining numbers on subsequent doses and older age, respectively 139 and 143, 96 and 103, 88 and 95 for second,

third and fourth dose (Table 5). Only 16 and 12 times DPTP was given singly, without simultaneous other vaccines. In both years only one report concerned HepB vaccination. In 1996 one child received DTP(olio) instead of the scheduled DPTP because of complex neuropathology. In 1997 two of the reported vaccinees received DTP in stead of the scheduled DPTP both because of prior adverse events, without there being a medical contra-indication.
In 1996 MMR was involved 99 times; MMR1, 88 times of which two were MMR0 (under the age of one year), in seven cases with simultaneous other vaccines; one child received its second MMR in an accelerated schedule at the age of 15 months. MMR2 was involved 11 times, once without (known) simultaneous DTP.
In 1997 MMR was involved 129 times of which 105 concerned MMR1 (twice before the age of one year) in 7 cases with simultaneous other vaccines; one child received MMR2 in an accelerated schedule at 14m of age. 24 reports were about MMR2 in all but one with simultaneous DTP of which three times the dose numbers were not known.
DTP revaccination at 4 years of age was involved 24 and 22 times respectively in 1996 and 1997 and the revaccination at school age 13 and 25 times (in both years once only MMR and once only DTP).

Table 5a. Schedule and vaccines of reported AEFI in 1996

vaccine given⇒ scheduled ⇓	dptp	dptp hib	hib	dptp hib mmr	dptp mmr	mmr	dtp	dtp mmr	hepb	bcg	unknown	total 1996	1995	1994
dptp-1+hib-1	4	279[a]	1	-	-	-	-	-	-	-	-	284	324	300
dptp-2+hib-2	3	136[b]	-	-	-	-		-	-	-	-	139	141	126
dptp-3+hib-3	3	91		-	2[c]	-		-	-	-	-	96	103	91
dptp-4+hib-4	5	77	-	4	1	-	1[d]	-	-	-	-	88	83	70
dptp-?+hib-?	1	3	-	-	-	-	-	-	-	-	-	4	9	2
mmr-1	-	-	-	-	-	80[e]	-	-	-	-	-	80	95	74
dtp-5	-	-	-	-	-	-	24	-	-	-	-	24	18	11
dtp-6+mmr-2	-	-	-	-	-	1	1[f]	11	-	-	-	13	21	21
hib catch-up	-	-		-	-	-	-	-	-	-	-	-	3	8
other	-	-	-	-	-	-	-	-	1	1	2	4	3	9
total	16	586	1	4	3	81	26	11	1	1	2	732	800	712

[a] once dptp1+hib2
[b] once dptp2+hib1
[c] once dptp3+mmr0 in child 7m old and once delayed dptp3+mmr1 in child 17m old
[d] once dtp4 in child with complex neuropathology
[e] once mmr0 in child less than one year old and once mmr2 accelerated schedule in 15m old child
[f] once catch up dtp2 in refugee child 7 years old

Table 5b. Schedule and vaccines of reported AEFI in 1997

vaccine given⇒ scheduled ⇓	dtpt	dptp hib	hib	dptp hib mmr	dptp mmr	mmr	mmr hib	dtp	dtp hib	dtp mmr	hepb	other	total 1997	1996	1995	1994
dptp-1+hib-1	4	318	1	-	-	-	-	-	-	-	-	-	323	284	324	300
dptp-2+hib-2	2	140	-	-	-	-	-	-	-	-	-	-	142	139	141	126
dptp-3+hib-3	-	102[a]	-	1[b]	-	-	-	-		-	-	-	103	96	103	91
dptp-4+hib-4	4	83	-	3	2	-	1	1	1	-	-	-	95	88	83	70
dptp-?+hib-?	2	6	-	-	-	-	-		-	-	-	-	7	4	9	2
mmr-1	-	-	-	-	-	98[c]	-		-	-	-	-	98	80	95	74
dtp-5	-	-	-	-	-	-	-	22[d]	-	-	-	-	22	24	18	11
dtp-6+mmr-2	-	-	-	-	-	1	-	1[e]	-	23[f]	-	-	25	13	21	21
hib catch-up	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	8
other	-	-	-	-	-	-	-	-	-	-	1[g]	5[h]	7	4	3	9
total	12	649	1	4	2	99	1	24	-	23	1	5	822	732	800	712

[a] once dptp3+hib2
[b] once dptp+hib3+mmr0
[c] once mmr0 and once mmr2 in accelerated schedule (12 and 15 months)
[d] once dtp3 in alternative schedule
[e] once dtp2 catch up dose in 11 year old immigrant
[f] three times dtp+mmr unknown dose numbers
[g] first dose
[h] influenza, measles, opv, yellow fever, ppd

Event categories are not equally distributed over the (scheduled) vaccinations (Table 6a and b). Faints, mainly collapse, and discoloured legs are most often reported after the first vaccinations, as is persistent screaming. Convulsions, especially febrile, are reported more often after the fourth DPTP/Hib and the first MMR. See for details the Paragraphs of the specific event categories (Paragraph 6.9).

Table 6a. Event category and (scheduled) vaccine dose of reported AEFI in 1996

vaccine⇒[a] event ⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/hib?	mmr1	dtp5	dtp6/mmr2	other	total 1996	1995	1994
local reaction	6	7	9	6	-	2	10	4	2	46	39	31
general illness minor	85	47	35	34	1	32	9	1	-	244	280	242
major	10	8	11	6	-	11	-	4	1	51	55	61
persistent screaming	10	3	2	1	-	-	-	-	-	16	22	37
skin symptoms	15	12	8	7	1	13	1	-	1	58	61	78
discoloured legs	53	34	8	2	1	1	-	-	-	99	93	43
faints[b]	87	19	18	3	-	-	4	3	-	134	147	141
fits[c]	12	7	4	28	1	20	-	1	-	73	97	74
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	1	1	-	-	-	-	-	2	1	-
death	6	2	-	-	-	1	-	-	-	9	5	5
total	284	139	96	88	4	80	24	13	4	732	800	712

[a] scheduled vaccines are listed. See for more precise description Table 5 and respective event categories
[b] collapse, breath holding spells and syncope
[c] convulsions, atypical attacks and epilepsy

Table 6b. Event category and (scheduled) vaccine dose of reported AEFI in 1997

vaccine⇒[a] / event ⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/hib?	mmr1	dtp5	dtp6/mmr2	other	total 1997	1996	1995	1994
local reaction	7	5	5	7	2	5	7	11	-	49	46	39	31
general illness minor	99	53	42	24	3	23	3	6	1	254	244	280	242
major	4	7	11	19	-	13	1	1	1	57	52	55	61
persistent screaming	17	8	-	-	-	-	-	-	-	26	16	22	37
skin symptoms	16	14	7	9	1	15	6	3	3	74	58	61	78
discoloured legs	60	18	15	-	1	1	-	-	-	95	99	93	43
faints[b]	106	26	11	5	-	-	4	2	1	155	134	147	141
fits[c]	14	11	11	30	1	38	1	2	-	108	73	97	74
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	-	-	1	-	-	-	1	1	1	-
death	-	-	-	1	-	2	-	-	-	3	9	5	5
total	323	142	103	95	8	98	22	25	6	822	732	800	712

[a] scheduled vaccines are listed. See for more precise description Table 5 and respective event categories
[b] collapse, breath holding spells and syncope
[c] convulsions, atypical attacks and epilepsy

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.

6.5 Feedback to Reporters

Feedback of diagnosis and causality with advice about further vaccinations is a major characteristic of the surveillance system. This feedback is increasingly done by telephone. In 1995 29% of reports got a full written account as opposed to 19 and 9% in 1996 and 1997 (Table 7).

Table 7. Feedback method and events of reported AEFI in 1995, 1996, 1997

event ⇓ / feedback method⇒		1995 written	1995 tel.	1995 total	1996 written	1996 tel.	1996 total	1997 written	1997 tel.	1997 total
local reaction		5	34	39	7	39	46	-	49	49
general illness	minor	59	221	280	21	223	244	3	251	254
	major	25	30	55	16	35	52	16	41	57
persistent screaming		3	19	22	1	15	16	-	26	26
skin symptoms		9	52	61	7	51	58	4	70	74
discoloured legs		13	80	93	14	85	99	4	91	95
faints		56	91	147	36	98	134	20	135	155
fits		58	39	97	29	44	73	25	83	108
anaphylactic shock		-	-	-	-	-	-	-	-	-
encephalopathy/-itis		1	-	1	2	0	1	1	-	1
death		5	-	5	8	1	9	3	-	3
total		234	566	800	141	591	732	76	746	822

6.6 Source of Information and Medical Intervention

In nearly half the notifications the reporter was the sole informant, in 51% information was received from others also (Table 8a and b). In 95% (1996) and 94% (1997) the clinics (child health care, school health and refugee clinics) supplied information. Parents were in 45% and 47% of cases contacted and sole informer of 10 and 24 reports; hospital specialists supplied information in 17% and 15% of reports in 1996 and 1997 respectively. For 1995 Figures were rather similar. In 1996, an insurance official requested information about possible compensation; this report could not be tracked down in our system and we did not receive the promised details. In 1997 the four ‘others’ as sole reporter were LAREB, MAE, a child health care administrator and a homeopath; none of these reports could be substantiated further because of lacking information.

Table 8a. Information sources and events of reported AEFI 1996

																total
info ⇒	clinic	+	+	+	+	+	+	+	+	-	-	-	-	-	-	699
	parent	-	+	+	+	+	-	-	-	+	+	-	-	-	-	333
	gen. pract.	-	-	-	+	+	-	+	+	+	-	+	-	-	-	68
	hospital	-	-	+	-	+	+	-	+	-	-	-	+	-	-	127
	other only	-	-	-	-	-	-	-	-	-	-	-	-	+	-	1
event ⇓	unknown	-	-	-	-	-	-	-	-	-	-	-	-	-	+	3
local reaction		20	15	1	2	1	1	1	-	-	-	3	1	-	1	46
general illness	minor	134	73	11	4	-	4	3	1	-	8	3	1	-	2	244
	major	19	12	6	1	3	4	2	2	-	-	-	1	1	-	51
persistent screaming		11	4	-	-	-	-	-	-	-	-	-	1	-	-	16
skin symptoms		28	24	1	1	-	1	-	-	-	1	2		-	-	58
discoloured legs		44	32	11	1	3	2	4	-	-	-	-	2	-	-	99
faints		51	48	19	4	1	8	1	-	-	1	-	1	-	-	134
fits		21	18	13	4	5	4	1	5	-	-	-	2	-	-	73
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-		-	-	-
encephalopathy/-itis		-	-	-	-	2	-	-	-	-	-	-	-	-	-	2
death		-	-	-	-	2	1	-	5	-	-	-	1	-	-	9
total		328	226	62	17	17	25	12	13	-	10	8	10	1	3	732

Table 8b. Information sources and events of reported AEFI 1997

															total
info ⇒	clinic	+	+	+	+	+	+	+	+	-	-	-	-	-	778
	parent	-	+	+	+	+	-	-	-	+	-	+	-	-	386
	gen. pract.	-	-	-	+	+	-	+	+	+	+	-	-	-	64
	hospital	-	-	+	-	+	+	-	+	-	-	-	+	-	126
event ⇓	other only	-	-	-	-	-	-	-	-	-	-	-	-	+	4
local reaction		31	11	-	-	-	1	1	-	1	2	2	-	-	49
general illness	minor	151	75	2	2	1	8	1	-	-	3	7	2	2	254
	major	22	12	3	-	8	4	-	2	1	-	4	-	1	57
persistent screaming		13	10	-	-	-	-	1	-	-	-	2	-	-	26
skin symptoms		33	22	2	3	2	3	1	-	1	2	4	1	-	74
discoloured legs		37	43	4	1	4	1	1	-	-	2	2	-	-	95
faints		46	80	15	3	3	4	1	-	-	-	3	-	-	155
fits		30	20	23	3	5	19	1	5	-	1	-	-	1	108
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		-	-	1	-	-	-	-	-	-	-	-	-	-	1
death		-	-	1	-	-		-	2	-	-	-	-	-	3
total		363	273	51	12	23	40	7	9	3	10	24	3	4	822

The impact of adverse events may also be illustrated by medical intervention received. In 36% and 35% of reported events no professional medical help was sought or was not recorded by us for 1996 and 1997 respectively; 55 and 82 parents administered paracetamol suppositories or (once) diazepam by rectiole. In more than half the events (52% and 54%) parents contacted the clinic or GP, called the ambulance, or went to hospital, with a little over 11% and 10 % admittance respectively. In 1995 these latter percentages were 53% and 11%. In Table 9a and b intervention is ordered according to highest level used.

Table 9a Medical intervention and events of reported AEFI in 1996

intervention⇒ event⇓	?	none[a]	supp[b]	clinic[c]	gp tel[d]	gp visit[e]	ambu lance[f]	out-patient	emerg ency	hospital stay	other	post mortem	total
local reaction	10	6	-	6	-	18	-	3	-	3	-	-	46
general illness minor	92	25	23	12	4	61	-	11	3	10	3	-	244
major	11	1	3	-	2	16	-	2	-	16	-	-	51
persistent screaming	4	1	4	-	1	4	-	1	1	-	-	-	16
skin symptoms	18	6	1	7	-	21	-	4	-	-	1	-	58
discoloured legs	26	10	16	6	4	22	-	7	4	4	-	-	99
faints	15	31	5	11	10	24	1	11	5	21	-	-	134
fits	7	2	3	1	3	18	6	7	6	20	-	-	73
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	-	-	-	-	-	-	2	-	-	2
death	1	1	-	-	-	-	-	-	-	2	-	5	9
total	184	83	55	43	24	184	7	46	19	78	4	5	732

[a] homeopathic or herb remedies, baby message 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 visit without transport to hospital

Table 9b Medical intervention and events of reported AEFI in 1997

intervention⇒ event⇓	?	none[a]	supp[b]	clinic[c]	gp tel[d]	gp visit[e]	ambu lance[f]	out-patient	emerg ency	hospital stay	other	post mortem	total
local reaction	16	5	1	9	-	15	-	2	1	-	-	-	49
general illness minor	75	30	43	13	12	44	-	24	1	6	6	-	57
major	10	1	7	1	1	14	-	4	1	15	3	-	254
persistent screaming	10	4	7	1	-	3	-	-	1	-	-	-	26
skin symptoms	16	6	1	8	4	27	-	6	2	3	1	-	74
discoloured legs	29	11	12	7	8	19	-	3	3	3	-	-	95
faints	23	37	9	7	15	30	5	9	5	14	1	-	155
fits	12	2	2	4	4	27	1	8	5	43	-	-	108
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	-	-	-	-	-	-	1	-	-	1
death	-	-	-	-	-	-	1	-	-	-	-	2	3
total	191	96	82	50	44	179	7	56	19	85	11	2	822

[a] homeopathic or herb remedies, baby message 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 visit without transport to hospital

6.7 Sex Distribution

Overall more boys (56% and 55% for 1996 and 1997) were reported than girls, similar to 1995, although a little lower percentage than in 1994 (60%). Distribution over the different events ranged from 49% (local reactions) to 66% boys (collapse) for 1996 and from 44% (discoloured legs) to 58% (collapse) for 1997 with the events with less than 30 reports excluded. See for specifics on the events and subdivision, the respective categories under Paragraph 6.9.
Under unknown are several cluster reports of minor illness, local reactions and unsubstantiated rumours (see Table 10).

Table 10. Events and sex of reported AEFI in 1996 and 1997

event ⇓		sex⇒	male	female	unknown	1996 total	male	female	unknown	1997 total
local reaction			21	22	3	46	22	26	1	49
general illness		minor	121	110	13	244	141	106	7	254
		major	28	21	2	51	33	24	-	57
persistent screaming			11	4	1	16	10	16	-	26
skin symptoms			29	27	2	58	46	28	-	74
discoloured legs			55	43	1	99	42	53	-	95
faints	collapse		78	40	2	120	84	60	1	145
	BHS		4	3	-	7	4	-	-	4
	fainting		5	2	-	7	2	4	-	6
fits	convulsions		21	19	2	42	31	27	-	58
	epilepsy		2	1	-	3	3	2	-	5
	atypical attacks		16	12	-	28	24	19	2	45
anaphylactic shock			-	-	-	-	-	-	-	-
encephalopathy/-itis			1	1	-	2	-	1	-	1
death			5	4	-	9	-	3	-	3
total			397	309	26	732	442	369	11	822

6.8 Causal Relation

Adverse reactions are events with (likelihood of) causality assessed as certain, probable or possible; in 1996 and 1997 that was the case in 78 and 80% of reports. The other events were considered coincidental events with improbable or absent causal relation with the vaccinations. 12 and 17 notifications were not classifiable (1.6% and 2 %). There are great differences in causality over the different event categories. On the one end persistent screaming with in 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 (one case could not be substantiated). For MMR vaccination only 40% of reported adverse events were considered an adverse reaction in 1996. For DTP, DPTP and Hib vaccinations this percentage was 81%. For 1997 these percentages were 53% (MMR) and 80% (DTP, DPTP and Hib). See for further specifics the event categories below (Paragraph 6.9).
In 1994 and 1995, overall 84% and 81% of reports were regarded adverse reaction.

Table 11a. Causality and events of reported AEFI in 1996

event ⇓	causality⇒	certain	probable	possible	improbable	non classifiable	total
local reaction		28	11	6	-	1	46
general illness	minor	-	96	78	67	3	244
	major	-	12	13	23	3	51
persistent screaming		-	16	-	-	-	16
skin symptoms		-	4	25	29	-	58
discoloured legs		-	89	9	1	-	99
faints	collapse	-	102	10	7	1	120
	BHS	-	5	2	0	-	7
	fainting	-	7	-	-	-	7
fits	convulsions	-	10	20	10	2	42
	epilepsy	-	-		3	-	3
	atypical attacks	-	5	16	6	1	28
anaphylactic shock		-	-	-	-	-	-
encephalopathy/-itis		-	-	1	1	-	2
death		-	-	-	8	1	9
total		28	357	180	155	12	732

Table 11b Causality and events of reported AEFI in 1997

event ⇓	causality⇒	certain	probable	possible	improbable	non classifiable	total
local reaction		36	6	6	1	-	49
general illness	minor	-	88	91	70	5	254
	major	-	9	23	25	-	57
persistent screaming		-	26	-	-	-	26
skin symptoms		-	2	37	33	2	74
discoloured legs		-	83	6	4	2	95
faints	collapse	-	128	13	4	-	145
	BHS	-	3	1	-	-	4
	fainting	-	6	-	-	-	6
fits	convulsions	-	10	33	11	4	58
	epilepsy	-	-		5	-	5
	atypical attacks	-	8	26	7	4	45
anaphylactic shock		-	-	-	-	-	-
encephalopathy/-itis		-	-	1	-	-	1
death		-	-	-	3	-	3
total		35	370	237	163	17	822

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 1996 or 1997.

6.9.1 Local reactions

In 1996 46 predominant local reactions were reported mainly after DPTP/Hib vaccinations. Mostly the symptoms were one sided but four times on either injection site. One report was not classifiable because of incomplete notification and lacking data on time interval. All other

reports were considered adverse reactions (Table 12a). Most often the symptoms were common local inflammation, seven times severe or prolonged some with atypical symptoms. 15 Children with mild or moderate local reactions had atypical symptoms; these included super-infection of local eczema, (possible) erysipelas, regional(?) lymphadenopathy. Some children had pain only, at the injection site, without other signs of inflammation and refused to use the limb or limped for some time. Of the four children with abscess one was culture positive (β haemolytic streptococcus A), on the others no culture was performed; one was definitely at the DPTP site and one was definitely at the Hib site and the other two were one-sided but not attributable. No faulty procedures were involved in these cases. MMR was involved only six times with twice a (possible) causal relation. Of the four times with simultaneous DTP three were ascribed to DTP and once the reaction was not classifiable.

Table 12a. Local reactions and vaccines of reported AEFI in 1996

vaccine⇒ event⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	mmr1	dtp5	dtp6/mmr2	hib	bcg	unknown	total
mild/moderate	3	2	5	2	-	4	3	-	-	1	20
severe/prolonged	-	-	-	1	1	4	-	-	1	-	7
abcess	1	1	1	1	-	-	-	-	-	-	4
atypical	1	4	3	2	1[a]	2	1	1	-	-	15
total	5	7	9	6	2	10	4	1	1	1	46

[a] once mmr dose number unknown

In 1997 49 of the reported cases had predominant local symptoms in all but one considered adverse reaction, mainly occurring after simultaneous DPTP/ Hib vaccinations, more often at DPTP/DTP site than at Hib site and five times at both sites. No abscesses were reported in 1997. 8 times the local reaction was considered severe, some with atypical symptoms. Of the mild and moderate reactions 13 had atypical symptoms. Sometimes there was only pain without signs of local inflammation. Three children stopped using the affected limb altogether and made a lame impression. Others had (de-) pigmentation at the injection site or blister, pustules, eczema or spider naevus etceteras (Table 12b). In 1997 MMR was involved 15 times; of the ten times MMR was given simultaneously with DTP, all local reactions occurred at the DTP site.

Table 12b. Local reactions and vaccines of reported AEFI in 1997

vaccine⇒ event⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/hib?	mmr1	dtp5	dtp6/mmr2	total
mild/moderate	5	2	2	5[a]	2[a]	2	3	7[c]	28
severe/prolonged	-	1	-	1	-	-	4[b]	2	8
abcess	-	-	-	-	-	-	-	-	-
atypical	2	2	3	1	-	3	-	2	13
total	7	5	5	7	2	5	7	11	49

[a] once dptp only
[b] once dtp3 alternative catch up schedule
[c] once unknown dose numbers and once dtp2 only in catch up schedule immigrant

6.9.2 Systemic symptoms

Events that are not classifiable in one of the other categories, above or below are listed under general illness. Depending on severity there may be subdivision in minor or major.

general minor illness

In 244 and 254 children the complaints were considered minor illness in 1996 and 1997, in 28% considered without causal relation with the vaccination in both years (in 1994 17% and in 1995 23%) (see also Table 11). 83% and 87% of reports concerned the scheduled DPTP/Hib vaccinations, most frequently events following the first DPTP/Hib (Table 13). For comparison the numbers of 1994 and 1995 are included. 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, 66 and 70, once low grade only in each year. Fever was also the most frequent symptom in the other diagnoses (93 and 92 times). Crying was the second most frequent main symptom (40 and 34), 26 and 19 times fierce, 13 and 11 times screaming and once and four times prolonged in 1996 and 1997 respectively. More often there was pronounced crying in the other events (65 and 66 times). Irritability was quite frequently diagnosed, as were chills and (sleeping) jerks, with or without fever, as often as main working diagnosis as accompanying symptoms. Pallor as sole symptom was quite frequent as well, as were gastro-intestinal complaints. Like other years there were a few children with bulging fontanel, twice in 1996 and four times in 1997, but only once with possible causality. In 1997 a couple of children with red urine (myoglobinuria?) are included in the minor illness category. See for further symptoms and causality Table 14.

Table 13. Minor illness and vaccines of reported AEFI in 1994-1997

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

[a] three times dptp only
[b] once dptp only
[c] once delayed dptp/hib3/mmr1, once dptp/hib4/mmr1 and once dptp4/mmr1
[d] once mmr0
[e] once unknown dose numbers and once mmr2 only
[f] hib4/mmr1

In 1996 36 times MMR was administered, either singly (32) or simultaneously (4) with other vaccines; the MMR vaccine was implicated as possible cause 13 times or 36%, (vaccinitis-11, fever-1, swollen cheek-1). The symptoms were likely to have been caused by the simultaneous DPTP (fever) once. The others were considered to be coincidental events. Thus with MMR a little more than one third of the reports in the category were considered possible side effects. For the other vaccines listed, this was approximately 76%.
In 1997 30 times events followed MMR vaccinations, seven times with simultaneous other vaccines. 14 Were considered coincidental and of the remaining reports 4 were possibly due to DTP (fever-2, listlessness-1 and rash-illness-1). Thus a possible causal relation with MMR was inferred in only 12 cases (40%) (vaccinitis-9, parotitis-1, fever-1, light sensitive eyes-1). For the other vaccines in this disease category causality was assessed in 73%.

Table 14. Main (working) diagnosis or symptoms in minor illness of reported AEFI in 1996 and 1997 (with number of adverse reactions)

symptom or diagnosis	1996	(adverse reaction)	1997	(adverse reaction)	symptom or diagnosis	1996	(adverse reaction)	1997	(adverse reaction)
fever	66	(52)	70	(59)	pallor	19	(18)	25	(25)
crying	40	(37)	34	(31)	cyanosis	1	(1)	1	(1)
irritability	7	(7)	11	(9)	jaundice	-	(-)	1	(-)
meningismus	3	(1)	-	(-)	flush	1	(1)	-	(-)
myoclonics	12	12)	10	(10)	rash illness	16	(-)	19	(1)
chills	12	12)	6	(6)	vaccinitis	11	(11)	9	(9)
bulging fontanel	1	(-)	4	(1)	tonsillitis	2	(-)	1	(-)
thrashing	1	(1)	-	(-)	otitis	1	(-)	-	(-)
asthma attack	2	(1)	6	(1)	parotitis	1	(-)	2	(1)
airway infection	4	(-)	8	(-)	swollen cheek	2	(1)	-	(-)
cough	3	(1)	3	(-)	swollen face	2	(1)	-	(-)
dyspnea/wheezing	1	(-)	2	(-)	lymphadenopathy	-	(-)	1	(-)
pseudocroup	-	(-)	3	(-)	food allergy	1	(-)	-	(-)
groaning	1	(1)	-	(-)	stomatitis	1	(-)	-	(-)
listlessness	-	(-)	3	(2)	choking	1	(-)	-	(-)
drowsiness	1	(1)	2	(2)	feeding difficulty	1	(1)	2	(2)
prolonged sleeping	3	(3)	3	(3)	vomiting	2	(1)	5	(3)
hypertrophy	1	(-)	-	(-)	diarrhoea	1	(-)	-	(-)
arthralgia	-	(-)	1	(-)	gastro-enteritis	7	(1)	10	(6)
lying still/frozen	7	(5)	2	(2)	proctitis	1	(-)	-	(-)
limpness	2	(2)	-	(-)	change in behaviour	1	(-)	2	(-)
low temperature	-	(-)	1	(1)	queer laugh	1	(1)	-	(-)
rolling eyes	-	(-)	1	(1)	myoglobinuria?	-	(-)	2	(2)
light sensitivity	-	(-)	1	(1)	urinary tract infection	1	(-)	-	(-)
strabismus	-	(-)	1	(-)	red scrotum	1	(-)	-	(-)
not specified	3	(1)	2	(-)					

major general illness

In 1996 and 1997 51 and 57 reports were classified as major general illness (55 and 61 in 1995 and 1994) (Table 15a and b). High fever of ≥40.5°C was the working diagnosis in 22 cases in each year and a pronounced symptom in 10 and 12 other events in this category. In other event categories there was high fever of ≥40.5°C in another 10 and 22 cases respectively. The distribution is more even over the scheduled vaccines than in the minor illness group. For causality see Table 16a and b.

Of the reported events in 1996 16 followed MMR vaccination, four times with simultaneous other vaccines. In only three cases there was judged to be a possible causal relation, in all instances MMR only. Once there was idiopathic thrombocytopenic purpura (ITP) en once high fever and rash in the appropriate period. The last child had low visual acuity when tested in her fourth year and had old scars of retinitis. After MMR1 vaccination she was ill for some time, but consulted the GP mainly for fever and upper airway symptoms. We assessed causality as possible because later on she was diagnosed with a rare cellular immune disorder, although there is no evidence of retinitis following the MMR vaccination. The remaining 13 events after MMR vaccinations were considered coincidental because of time interval or established other cause.

In 1996 35 reported events followed (scheduled) DPTP/Hib vaccinations with 21 times (possible) causal relation with vaccine or vaccination. For the other events different causes have been established satisfactorily. The three sepsis were caused by campylobacter infection en twice meningococcus type B. There were three rumours this year that we could not substantiate, despite extensive search (MAE, GGD, CB and hospital). This concerned a cluster of diabetes cases after second MMR vaccination causing public unrest at the time of mass revaccination in the area. Another was a coming liability claim because of arthritis following DTP6/MMR2 and the third was a rumour of a cluster of severe illness with sequelae in the same family, after a congress of an anti-vaccination movement.

In 1997 18 events followed MMR vaccination, five times with other simultaneous vaccines, with in nine cases possible causal relation. Four times this was high fever and a rash in the appropriate time period. One child had high fever and one myoclonics with high fever. Of the four children with ITP, one was considered coincidental because of the long time interval and possible other cause. In one child with simultaneous other vaccines the high fever was attributed to DPTP/Hib, in the others the fever was considered not causally related with any of the vaccines.

In 1997 39 events followed DPTP, Hib or DTP vaccinations, with in 24 cases assessed causality. This was 19 times fever and twice excessive crying, once diarrhoea and once irritability. For the other events the time interval was not plausible or other causes had been established; these were considered to be coincidental.

Table 15a. Major illness and vaccines of reported AEFI in 1996

diagnosis⇓ vaccine⇒	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	mmr1	dtp6/mmr2	unknown	total
high fever	4	5	5[a]	5	3	-	-	22
arthritis	-	1[b]	-	-	-	1[c]	-	2
appendicitis	-	-	-	-	-	1	-	1
coxitis	1	-	-	-	1	-	-	2
pneumonia/bronchitis	1	1	-	-	-	-	-	2
rash illness	1	-	1	-	1	-	-	3
vaccinitis	-	-	-	-	1	-	-	1
sepsis	1	-	1	-	-	1	-	3
meningitis	-	-	-	1	-	-	-	1
chills	-	-	2	-	-	-	-	2
aplastic anaemia	-	-	-	-	1	-	-	1
ITP	-	-	-	-	1	-	-	1
acute cerebellar ataxia	-	-	-	-	1[d]	-	-	1
dehydration	-	1	1[b]	-	-	-	-	2
diabetes mellitus	-	-	-	-	1	1	-	2
osteomyelitis	1	-	-	-	-	-	-	1
irritability	1	-	-	-	-	-	-	1
myoclonics	-	-	1	-	-	-	-	1
retinitis	-	-	-	-	1	-	-	1
unsubstantiated rumour	-	-	-	-	-	-	1	1
total	10	8	11	6	11	4	1	51

[a] once dptp3/mmr0
[b] once dptp only
[c] unknown dose numbers
[d] once mmr2 in accelerated schedule at 15 months of age

Table 15b. Major illness and vaccines of reported AEFI in 1997

diagnosis⇓ vaccine⇒	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	mmr1	dtp5	dtp6/mmr2	ppd	total
high fever	4[a]	4	4	9[c]	1	-	-	-	22
arthritis	-	-	-	1[a]	2	-	-	-	3
rash illness	-	-	2	2	1	-	-	-	5
chickenpox	-	-	-	1	-	-	-	-	1
vaccinitis	-	-	-	-	3	-	1	-	4
sepsis	-	1	-	-	-	-	-	-	1
meningitis	-	-	1	-	1	-	-	-	2
airway infection	-	-	-	1	-	-	-	-	1
brain abscess	-	-	1	-	-	-	-	-	1
ITP	-	-	-	-	4	-	-	-	4
acute cerebellar ataxia	-	-	-	-	-	1	-	-	1
deafness	-	-	-	1[d]	-	-	-	-	1
kawasaki	-	-	-	1[d]	-	-	-	-	1
diarrhoea	-	1	1[b]	-	-	-	-	-	2
hepatitis	-	-	-	1	-	-	-	-	1
irritability	-	-	-	1	-	-	-	-	1
crying	-	1	1	-	-	-	-	-	2
myoclonics	-	-	-	-	1	-	-	-	1
plexus neuritis	-	-	1	-	-	-	-	-	1
blindness	-	-	-	-	-	-	-	1	1
pervasive disorder	-	-	-	1[a]	-	-	-	-	1
total	4	7	11	19	13	1	1	1	57

[a] once dptp only
[b] once dptp/hib/mmr0
[c] once dptp/hib/mmr1 and once dtp only
[d] once dptp/mmr1

Table 16a. Major illness and causal relation of reported AEFI in 1996

diagnosis⇓ causality⇒	certain	probable	possible	improbable	unclassifiable	total
high fever	-	9	9	4	-	22
arthritis	-	-	-	1	1	2
appendicitis	-	-	-	1	-	1
coxitis	-	-	-	2	-	2
pneumonia/bronchitis	-	-	-	2	-	2
rash illness	-	-	-	3	-	3
vaccinitis	-	-	1	-	-	1
sepsis	-	-	-	3	-	3
meningitis	-	-	-	1	-	1
chills	-	2	-	-	-	2
aplastic anaemia	-	-	-	1	-	1
ITP	-	-	1	-	-	1
acute cerebellar ataxia	-	-	-	1	-	1
dehydration	-	-	1	1	-	2
diabetes mellitus	-	-	-	1	1	2
osteomyelitis	-	-	-	1	-	1
irritability	-	-	-	1	-	1
myoclonics	-	1	-	-	-	1
retinitis	-	-	1	-	-	1
unsubstantiated rumour	-	-	-	-	1	1
total	-	12	13	23	3	51

Table 16b. Major illness and causal relation of reported AEFI in 1997

diagnosis⇓ causality⇒	certain	probable	possible	improbable	unclassifiable	total
high fever	-	8	11	3	-	22
arthritis	-	-	-	3	-	3
rash illness	-	-	-	5	-	5
chickenpox	-	-	-	1	-	1
vaccinitis	-	-	4	-	-	4
sepsis	-	-	1	-	-	1
meningitis	-	-	-	2	-	2
airway infection	-	-	-	1	-	1
brain abscess	-	-	-	1	-	1
ITP	-	-	3	1	-	4
acute cerebellar ataxia	-	-	-	1	-	1
deafness	-	-	-	1	-	1
kawasaki	-	-	-	1	-	1
diarrhoea	-	-	1	1	-	2
hepatitis	-	-	-	1	-	1
irritability	-	-	1	-	-	1
crying	-	1	1	-	-	2
myoclonics	-	-	1	-	-	1
plexus neuritis	-	-	-	1	-	1
blindness	-	-	-	1	-	1
pervasive disorder	-	-	-	1	-	1
total	-	9	23	25	-	57

6.9.3 Persistent Screaming

In 1996 and 1997 16 and 26 children with persistent screaming were reported (in 1994 and 1995 34 and 22). Over 1996 three children with persistent screaming are not included but categorised elsewhere (discoloured legs). For 1997 two children were not included and categorised under discoloured legs or collapse reaction. In four and nine cases there was also fever on the day of vaccination. As was noticed in former years this reported adverse event seems age/dose dependent (see Table 6 and 13). Local symptoms were pronounced in only seven and nine cases, of which two and five mainly had (presumed) pain at the injection site. Some children had both sided local reactions. Additional symptoms were restlessness, change in sleeping behaviour, pallor, vomiting, feeding difficulty, eye turning, irritability and myoclonics. Three and two children had no other symptoms at all. Parents were usually desperate and five contacted the family physician and two went to hospital in 1996. We did not record the degree of intervention in four cases, however. In 1997 six parents sought professional help, but we failed to record intervention in ten cases.
In all children there was a possible or probable likelihood that the vaccination was causally related with the event.

6.9.4 General skin manifestations/phenomenon

In 1996 and 1997 skin symptoms were the main or only feature in 58 and 74 reports. Discoloured legs are not included but categorised separately. The distribution over the different vaccine doses is rather similar in both years, most frequently following the first two DPTP/Hib vaccinations and the first MMR. See Table 17a and b.
In 1996 there were five children with petechial rash on upper body and face. Children with petechiae on the legs only are categorised under discoloured legs. 13 cases concerned MMR, with 7 times possible causal relation. Six times on the day of the vaccination and once after two weeks. The other events were considered not causally related with the vaccination. For the other vaccines, (possible) causal relation was assessed in 24 out of 45 events.

Table 17a. Skin symptoms and vaccines of reported AEFI in 1996

vaccine⇒ / symptoms⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/hib?	mmr1	dtp5	hepb3	total
angio-edema	1	2	-	-	-	1	-	-	4
vesicles	1	-	1	-	-	1	-	-	3
exanthema	6	4	2	5	-	6	-	-	23
erythema circumscript	1	-	-	-	-	-	-	-	1
harliquin	1	1	-	-	-	-	-	-	2
urticaria	2	1	2	2	-	4	1	1	13
eczema	2	1	1[a]	-	1[a]	-	-	-	5
chickenpox	-	-	-	-	-	1	-	-	1
swollen scar	-	1	-	-	-	-	-	-	1
petechiae	1	2	2	-	-	-	-	-	5
total	15	12	8	7	1	13	1	1	58

[a] one time dptp only

Table 17b. Skin symptoms and vaccines of reported AEFI in 1997

vaccine⇒ / symptoms⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/hib?	mmr1	dtp5	dtp6/mmr2	other	hepb1	total
angio-edema	2	2	1	1	-	2	1	-	-	-	9
vesicles/bullae	-	-	-	-	-	3	-	-	1[b]	-	4
exanthema	5	9	4[a]	5	-	4	1	-	-	1	29
erysipelas/cellulitis?	1	-	-	-	-	-	-	-	-	-	1
harliquin	-	1	-	-	-	-	-	-	-	-	1
urticaria	4	1	-	2	1	5	4	3[d]	1[c]	-	21
eczema	4	1	2	-	-	1	-	-	-	-	8
swollen groin	-	-	-	1	-	-	-	-	-	-	1
total	16	14	7	9	1	15	6	3	2	1	74

[a] one time dptp3/hib2
[b] yellow fever vaccine
[c] influenza vaccine
[d] once unknown dose number

In 1997 no children with petechial rash were reported, apart from those under discoloured legs. 18 Reports were of events following MMR vaccination of which three with simultaneous DTP. In these latter cases there were urticaria within one day that could not be attributed to a specific vaccine. Of the other events ten were considered with possible causal relation with MMR and the remaining five coincidental.
For the other vaccines 30 out of 59 reports were considered coincidental including the reports following HepB, Yellow Fever and Influenza vaccine.

Table 18a. Skin symptoms and causal relation of reported AEFI in 1996

causality⇒ / symptom⇓	certain	probable	possible	improbable	unclassifiable	total
angio-edema	-	1	2	1	-	4
vesicles	-	-	1	2	-	3
exanthema	-	1	9	13	-	23
erythema circumscript	-	-	-	1	-	1
harliquin	-	1	1	-	-	2
urticaria	-	-	6	7	-	13
eczema	-	1	2	2	-	5
chickenpox	-	-	-	1	-	1
swollen scar	-	-	-	1	-	1
petechiae	-	-	4	1	-	5
total	-	4	25	29	-	58

Table 18b. Skin symptoms and causal relation of reported AEFI in 1997

causality⇒ / symptom⇓	certain	probable	possible	improbable	unclassifiable	total
angio-edema	-	-	4	4	1	9
vesicles/bullae	-	-	1	2	1	4
exanthema	-	-	14	15	-	29
erysipelas/cellulitis?	-	-	-	1	-	1
harliquin	-	-	1	-	-	1
urticaria	-	2	13	6	-	21
eczema	-	-	3	5	-	8
swollen groin	-	-	1	-	-	1
total	-	2	37	33	2	74

6.9.5 Discoloured legs

Starting from 1995, a separate category is discoloured legs. These are 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 reported separately.
In 1996 and 1997 a total of 99 and 95 reports came in (93 in 1995).
In 1996 there were 18 blue legs (11 double sided), 41 red legs (29 double sided) and 27 purple legs (20 double sided). Of the 14 one-sided discoloration three were on the Hib leg and seven on the DPTP leg, and in four cases this could not be decided. In total, 31 children had petechiae, including 12 reports without noted prior discoloration of the legs; 21 times double sided and ten times one sided of which twice on the Hib side, five times on the DPTP side and once unknown and once mainly on the breast (Table 19a).
About 20% of the children had also fever of which two more ≥40.5°C. Over half the children exhibited fierce crying of whom four for several hours (three times possibly persistent screaming, not listed seperately). Injection site reactions, if any were not pronounced, but 14 times pronounced pain was noted without other signs of inflammation. Six children had also collapse reaction, and one an atypical attack, possibly chills. These compound reports are listed under the other respective categories also. Eight of the children had recurrent discoloured legs. Reports of discoloured legs were most frequent after the first DPTP/Hib vaccinations and decreasing in number with dose/age.
Causal relation with the vaccines was inferred in all but one case. See Table 11a.

Table 19a. Discoloured legs and vaccines of reported AEFI in 1996

symptoms⇓ vaccine⇒	dptp/hib1	dptp/hib2	dtpt/hib3	dptp/hib4	dptp/hib?	mmr1	(petechiae)	total
blue legs	11	5	2	-	-	-	(1)	18
red legs	24	12	2	2	-	1	(11)	41
purple legs	13	12	2	-	-	-	(6)	27
petechiae only	5[a]	5[a]	2	-	1	-	(12)	12
total	53	34	8	2	1	1	(31)	99

[a] once dptp only

In 1997 reports concerned blue legs 23 times (twice one-sided), red legs 38 times (one-sided 9) and purple legs 23 times (one-sided 4). See Table 19b.

Table 19b. Discoloured legs and vaccines of reported AEFI in 1997

symptoms⇓ vaccine⇒	dptp/hib1	dptp/hib2	dtpt/hib3	dptp/hib4	dptp/hib?	mmr1	(petechiae)	total
blue legs	14	6	3	-	-	-	(3)	23
red legs	25[a]	6	6	-	-	1	(12)	38
purple legs	15	4	4	-	-	-	(7)	23
petechiae only	6	2	2	-	1	-	(11)	12
total	60	18	15	-	1	1	(30)	95

[a] once hib only

Petechiae were reported 30 times, 11 times without noted prior discoloration. Fierce crying accompanied the discoloration in 74 cases, two of which prolonged (once possibly persistent screaming not listed seperately). Seven reports were compound, six times also collapse reaction and once an atypical attack. These events were booked separately under these respective categories. Four of the children had recurrence of discoloured legs after subsequent vaccination.
In 1997 discoloured legs are most frequently reported after the first vaccinations and decreasing with dose/age (as in 1995 and 1996). Four times the event was assessed not related to the vaccination and twice causality could not be determined because of lacking information. All other events were considered to be a (possible) adverse reaction (89). See Table 11b.
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 20a and b). In 1996 there were 120 collapse cases, seven times BHS and seven fainting in older children. The seven children with BHS turned blue, after stopping to breath in expiration when fierce crying, with very short phase of diminished responsiveness and no limpness or pallor.
In 1997 there were 145 collapse cases and 4 times BHS. Six times there was fainting in older children.
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.

Table 20a. Faints and vaccines of reported AEFI in 1996

event⇓ vaccine⇒	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dtp5	dtp6/mmr2	total
collapse	84[a]	17[b]	16	3	-	-	120
breath holding spell	3	2	2	-	-	-	7
fainting	-	-	-	-	4	3	7
total	87	19	18	3	4	3	134

[a] once dptp1/hib2
[b] once dptp2/hib1

Table 20b. Faints and vaccines of reported AEFI in 1997

event⇓ vaccine⇒	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	measles	dtp5	dtp6/mmr2	total
collapse	105[a]	24	10	5	1	-	-	145
breath holding spell	1	2*	1	-	-	-	-	4
fainting	-	-	-	-	-	4	2	6
total	106	26	11	5	1	4	2	155

[a] once dptp only

In 1996 there was one recurrent incomplete collapse reaction, once possible atypical recurrence after the fourth DPTP/Hib vaccinations. One child had another BHS after a subsequent vaccination. Seven collapse cases were considered not related because of the too long time interval. Once causality could not be determined because of lacking information. See also Table 10 and Table 11a for sex distribution and causality.
In 1997 one child had recurrent collapse reaction, after the second dose, though of shorter duration and less complete. Four times the collapse reaction was considered to be coincidental, because of the time interval of several days. See also Table 10 and Table 11b 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.
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 21a and b). 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 22a and b). Of the four children with non-febrile convulsions in 1996, three occurred after DTP or MMR; one had epilepsy, but had stopped medication and the other two had neurological problems before. Altogether 7 children had fever of over 40.5°C, twice in children with atypical attacks and 5 times with convulsions.

In 1997 there were also four children with non-febrile convulsions of which two had epilepsy. In 1997 in this category there was 19 times very high fever of $\geq$ 40.5°C, seven in the atypical attacks and 12 in the convulsions.

Table 21a. Fits and vaccines of reported AEFI in 1996

event ⇓ vaccine ⇒	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/hib +mmr	dptp/hib?	mmr1	dtp6/mmr2	total 1996	total 1995	total 1994
febrile convulsion simple	1	1	-	10[a]	1	1	10	-	24	23	27
complex	-	-	-	5[a]	1	-	2	-	8	18	20
tonic	-	-	-	1	-	-	2	-	3	10	n.r
atypical	-	1[a]	-	-	-	-	2	-	3	7	3
non febrile convulsion	-	1	-	1[c]	-	-	1	1[b]	4	6	5
epilepsy	1	1	1	-	-	-	-	-	3	3	3
atypical attack	10	3	3	9	-	-	3	-	28	30	16
total	12	7	4	26	2	1	20	1	73	97	74

[a] once dptp only
[b] once dtp2 catch up dose in refugee catch up dose in eight year old
[c] once only dtp administered.

Table 21b. Fits and vaccines of reported AEFI in 1997

event ⇓ vaccine ⇒	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/hib +mmr	dptp/hib?	mmr1	dtp5	dtp6/mmr2	1997	1996	total 1995
febrile convulsion simple	-	-	2	8	1	-	16	-	-	27	24	23
complex	1	1	-	6	1	-	9	-	-	18	8	18
tonic	-	1	-	-	-	-	-	-	-	1	3	10
atypical	-	-	-	1	-	-	4	1	1[b]	7	3	7
non febrile convulsion	2	1	-	1[a]	-	-	1	-	-	5	4	6
epilepsy	-	-	2	2	-	-	1	-	-	5	3	3
atypical attack	11	8	7	10	-	1	7	-	1	45	28	30
total	14	11	11	28	2	1	38	1	2	108	73	97

[a] once only dtp4/hib4 administered.
[b] once mmr2 only

Table 22. Fits and fever of reported AEFI in 1996 and 1997

	1996				1997			
event⇒	convulsions		atypical attacks		convulsions		atypical attacks	
vaccine [a] ⇓	<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	8	2	2	1	7	4
dptp/hib2	1	2	1	2	1	2	5	3
dptp/hib3	-	-	1	2	-	2	2	5
dptp/hib4	-	16	3	6	1	16	4	6
dptp/hib?	2	-	-	-	-	-	1	-
dptp/hib+mmr	-	2	-	-	-	1	-	-
mmr1	3	14	1	2	5	25	-	7
dtp5	-	-	-	-	-	1	-	-
dtp6/mmr2	1	-	-	-	1	-	1	-
total	7	35	14	14	10	48	20	25

[a] scheduled vaccines, for more specifics see Table 21

See for sex distribution and causality Table 10 and tables 11a and b.
In 1996 70% of the events were considered possible adverse reaction. For atypical attacks this was 75% and for convulsions 71%. For 1997 71% of the events had a possible causal relation with the vaccination (atypical attacks 76% and convulsions 74%). None of the reported epilepsies were regarded as caused by the vaccination in either year (tables 11a and b).
MMR was involved in 22 reports in 1996. In 20 cases MMR was administered as single vaccine, with inferred causal relation in ten; in the two simultaneous DPTP/Hib/MMR once the event was attributed to MMR and once to DPTP/Hib. Thus there was causal relation for MMR in 55% and for the other vaccines in 76% of cases.
In 1997 42 events followed MMR vaccination, three times given simultaneous with other vaccines. 26 Times the event was attributed to MMR given singly and once to MMR in combination with DPTP/Hib (68%). For the other vaccines causality was assessed as possible or probable in 82% of the events.

6.9.8 Encephalopathy/encephalitis

In 1996 there was two cases of possible encephalitis after MMR vaccination. A girl received combined DPTP/Hib/MMR1 at the age of 14 months and developed fever eight days later. She was hospitalised because of a complex febrile convulsion. She recovered but a few days later she had an unexplained regression and had multiple convulsions and was subcomatose with signs of encephalopathy for a few days. Slowly she came out of this but stayed severely retarded. Causal relation with MMR vaccine could not be ruled out.
A boy of five months old got his third DPTP/Hib vaccinations. There were no complaints until five days later when he developed fever and became increasingly ill in the following days with diminished consciousness. Seven days after the vaccination he was hospitalised with convulsions which lasted for hours; he was comatose for seven days. EEG, CT and MRI were suggestive of encephalitis, suggestive of focal infection. He recovered slowly, but not without sequelae. A definite cause could not be established. The time interval and the symptoms do not fit causal relation with the vaccinations.
In 1997 there was one girl with encephalitis/encephalopathy. She received her MMR1 vaccination at 15 month of age and had eight days later fever that subsided in a few days. 19 days after the vaccination she developed very high fever and had a convulsive status for several hours. Despite intensive treatment she deteriorated and was comatose for a long time. There were permanent sequelae; the girl is brain damaged. Reye syndrome could not be excluded definitely and there were also signs of enterovirus infection. Causality was assessed as possible although the time interval was regarded as a little too long.

6.9.9 Anaphylactic shock

No cases were reported in 1996 and 1997. In matter of fact, we never received notification of anaphylactic shock with inferred causality and/or appropriate time interval, since the surveillance system was installed.

6.9.10 Death

In 1996 nine notifications came in of children who died after a vaccination of the RVP (Table 23a). There were five boys and four girls. The events were not considered to be caused or aggravated by the vaccine in all cases, nor was there an undue delay in diagnosis or therapy because of the vaccination. In one case the information could not be substantiated but the time interval makes causal relation unlikely.
Once parents were the reporters long after the death of their child because they had second thoughts about the vaccinations and questioned vaccinations of a younger sibling.

Table 23a. Death and vaccines of reported AEFI in 1996

child	sex	age	vaccines	time interval		symptoms/diagnosis	causality*	autopsy
				illness	death			
A	female	3 months	dptp/hib1	-	13 days	common cold, clinical sids	no	no
B	male	4 months	dptp/hib2	-	70 hours	sids	no	yes
C	female	4 months	dptp/hib1	?	≥7 days	down syndrome, no details	nd	?
D	female	3 months	dptp/hib1	-	<1 day	sids	no	yes
E	male	2 months	dptp/hib1	-	1 week	sids	no	yes
F	male	4 months	dptp/hib2	1.5 days	3.5 weeks	pneumococcal meningitis	no	no
G	male	3 months	dptp/hib2	3 days?	3.5 weeks	dehydration, toxic shock possibly campylobacter infection	no	no
H	female	15 months	mmr1	4 months	6 months	congenital cardiomyopathie, cardiac arrest	no	yes
I	male	3 months	dptp/hib1	5 weeks	13 months	leukaemia	no	no?

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

Child A, a girl received the first DPTP and Hib vaccinations at 3.5 months of age. She had some fever and local reactions for two to three days. After that there was a period with intermittent upper airway symptoms. Thirteen days after the vaccinations she was found dead in bed. The day before she had been more listless than usual, but not sick. Cultures of swabs and cerebrospinal fluid were negative. There was no autopsy performed.
Child B was four and a half months old when he received his second DPTP/Hib vaccinations. He experienced slight fever on that day, with full recovery the next day. On the third day after the vaccinations (70 hours) he was found cyanotic in his bed at the day care centre. Resuscitation was not successful. Autopsy revealed no abnormalities.
Child C was a girl with Down syndrome. She died at the age of four months and a half. In the calendar month before she had received her first vaccinations. This case could not be substantiated further.
Child D, a girl of 3 months old, got her first DPTP/Hib vaccinations. Afterwards she cried more and therefor the mother took her into her own bed. That night at approximately two o'clock she was found dead lying in prone position. Autopsy revealed no abnormalities.
Child E was a boy of three months old when he received his first DPTP/Hib vaccinations. He died a week later. We have no information on the immediate period after the vaccinations,

but the day before his death he was well. Autopsy revealed several abnormalities possibly (partly) caused by perinatal asphyxia and recent viral (RSV) infection. Cerebrospinal fluid had elevated white cell count, compatible with viral meningitis. CSF cultures were negative. The found abnormalities could not explain death.
Child F, a boy of four months old, received his second DPTP/Hib vaccinations. At the time of the vaccinations he had a slight cold and did not finish his bottles altogether. In the evening of the next day he developed fever. For which he got a paracetamol suppository. Fever remitted and he became increasingly ill, four days after the vaccinations he was admitted in hospital with convulsions. He had pneumococcal meningitis of which he died three weeks later.
Child G was a boy of three and a half months old, which received his second DPTP/Hib vaccinations together with his twin brother. In the days before he had had diarrhoea but was not ill at the time of vaccination. Three days later he was admitted in hospital with symptoms of dehydration, gastro-enteritis and fever. After initial stabilisation the situation deteriorated subsequently and after three weeks he succumbed because of respiratory insufficiency, metabolic acidosis and progressive liver failure. No autopsy was performed. His brother was a little less severely ill and recovered. From him campylobactor was isolated.
Child H was one year and nine months old when she died because of cardiac arrest in a state of irreversible brain damage. Two month before she had had her first cardiac arrest with progressive cardiomyopathy nearly four months after MMR vaccination. Post-mortem revealed a rare congenital possibly genetic primary cardiomyopathy with arrhythmias.
Child I was a boy that received his first DPTP/Hib vaccinations when 3 months old. Five weeks later he was diagnosed with leukaemia (pro B-cell ALL). Intensive treatment did not result in complete remission and the boy died at the age of one year and seven months.

In 1997 three children were reported, all girls. None of the cases were considered to be causally related to the vaccinations. As in 1996 one child was reported long after she had died because parents were unsure about the role of the vaccinations and were making up their minds about vaccinations of a younger child.

Table 23b. Death and vaccines of reported AEFI in 1997

child	sex	age	vaccines	time interval		symptoms/diagnosis	causality*	autopsy
				illness	death			
A	female	14	mmr1	12 days	13 days	waterhouse friderichsen, meningococcal infection, typeB	no	yes
B	female	12 months	dptp/hib4	-	9 days	sids	no	yes
C	female	15 months	mmr1	14 days	14 days	meningococcal septicaemia, typeB	no	no

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

Child A was a 14 months old girl that received her MMR vaccination. Five days later she was somewhat listless and touchy from which she recovered in a couple of days. 12 days after the vaccination she had a chill and passed greyish loose stool. When the GP was consulted she had 37.4°C and slight conjunctivitis of the left eye. In the evening she vomited twice but was not very ill otherwise. That night she started groaning and was taken into the mother's bed. The following morning she had died. Autopsy showed Waterhouse Friderichsen syndrome with positive cultures for meningococcus type B of CSF and spleen.
Child B was a 12 months old girl, which received the fourth DPTP/Hib vaccinations. There was some local reaction for two days but no fever. Nine days after the vaccinations she was put to bed perfectly healthy, apart from a slight cold. Two hours later she was found dead in prone position with her face down. Extensive post-mortem investigation did not reveal cause of death.
Child C was 15 months old when she received the MMR vaccination. The first signs of illness were 14 days later when she developed high fever, with a slight common cold. When the GP examined her there were a few petechiae. She was referred to hospital. On arrival she was in shock and on the way to a specialised care centre she died in the ambulance. Cultures of CSF and blood were positive for meningococcus type B.

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 [15]. The RVP is embedded in regular child health care with near total coverage, so the programme is delivered by a relative small group of specifically trained professionals. This is also advantageous for safety surveillance. The existence of a 24 h 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.

7.1 Increase in Number of Reports

There appears to be a steady increase in numbers of reported AEFI, although numbers should be interpreted with caution since they are estimates and not counts up till 1993. But nevertheless there seems to have been an actual increase with a levelling off in 1996 and 1997. In 1987 and 1993 vaccines have been added to the programme and 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 reported events that are coincidental but regarded as possibly related with the new and yet unknown vaccines. Reporting criteria have not been changed over the years, but awareness of the professionals and the public has increased lately, not only by the publicity around the newly introduced vaccines. Recently the need for vaccinations and the safety have been questioned in certain groups in the population and the public awareness of the severity of the target diseases has diminished now that the illnesses are effectively prevented by the vaccinations; this does increase the relative importance of side effects. This may influence the willingness to report possible adverse reactions as well. The vast majority of notifications is from Child Health Clinic staff, with a small rise in reports from parents although low in absolute numbers. The distribution over the different vaccine(dose)s and over the different event categories is similar to 1994 and 1995 (Table 5 and 6). Only the newly introduced category of discoloured legs stands out. We will discuss that under Paragraph 7.8.2.

7.2 Reporting Route

As in former years, the majority of notifications is by telephone. This is of great advantage because a substantial part of the reports are posed as a question or spring from the need of advice, also in case of the more severe events, even with inferred causality. Reporters tell us

that for them the reporting by telephone is less time consuming, and they appreciate the availability of direct consultation. We fear that with dividing this system in two, with reporting address and consultation service separated will result in a tremendous loss of reports as well as in the quality of the reports. Moreover it will cost more resources because of less efficiency and/or it will mean loss of expertise and quality of the services. Unfavourable experience in other countries should be taken to heart (for instance Denmark and Canada and Sweden) [16].
Reporting by telephone has an additional advantage; it possesses the opportunity to clarify some of the data and to get some necessary additional information. The events reported by mail, whether discharge letters or report forms, are never complete enough to allow adequate diagnosis and causality assessment straight away. The quality of data is very diverse and often there is only a pre-interpreted diagnosis without noting the accurate symptoms involved. We always need to get further information and contacting the reporter and others involved prove to be much more time consuming than with initial reporting by telephone. Even when detailed special forms are used, our own structured special questionnaire included, the information needed depends so much on vaccine, age and type and severity of the event, that this can not be covered by one single form. Mandatory forms may delay reporting and may diminish reporting rate, since they are more time consuming for the reporter as well.

7.3 Underreporting

Lowering underreporting is of special importance in passive surveillance systems, especially of selective underreporting. As explained above the telephone service is an important tool. Feedback and follow up are important too, in this respect. Although it has been put that the rise in numbers appears to be due to diminished underreporting, some underreporting will have to be accepted. Both adverse events that are regarded as evident adverse reactions and events that are regarded as evidently coincidental have more risk of not being reported. With the skipping of several contra-indications some adverse events may not be reported any more since the exact diagnosis is of no importance to subsequent vaccinations. It is important to watch out for this tendency because trend analyses or comparing different vaccines, schedules or vaccine lots may be jeopardised. But most of all selective underreporting of important adverse events must be avoided. The level of underreporting seems to be satisfactorily low, but we have to be vigilant all the same, and some specific events need increased attention. See sub paragraphs below.

7.3.1 Reporters

Most notifications came from Child Health Clinic staff and the rise in number is near totally attributable to the clinics. Nearly half the children were seen by their GP or in hospital because of the event, only 72 and 58 were reported by them in 1996 and 1997 respectively. We do not feel that this results in substantial loss of notifications because there is always the

safety net of the clinic where is asked after adverse events specifically. Sometimes however the clinic staff assumes that the GP or paediatrician will have reported the event, or if not, it is apparently not important to do so. Reporting by hospital staff or GP is however of advantage because notifications are earlier received with a more close signal detection and more accurate information without selective memory problems. Even if the adverse event will not be missed altogether, the reporting by GP or Hospital may save time because the event can be evaluated before the next clinic visit with unambiguous advice. One of the pitfalls is that the illness is inadvertently thought to be vaccine related and that there is an undue delay in diagnosis/recognition of an unrelated coincidental disease with (too) late treatment. On the other hand clear-cut collapse reactions must not be treated as anaphylactic shock or as ALTE (Apparent Life Threatening Event or near-SIDS) with the whole diagnostic protocol worked through.
Especially events after MMR1 may be missed more often. The clinic visits after MMR are much more time spaced and the applicable interval after the vaccination is wider and much less precise. Events following the booster vaccinations at four and nine years are not asked after at all since there is no further clinic visit. May be specific education of clinic staff in this respect is warranted and/or instructing parents to contact the clinic in case some unexpected or severe events occur.
GP's and also paediatricians need extra attention in educational activities on adverse events and contra-indications of the vaccination programme.

7.3.2 Geographical Distribution

The distribution of the reporting rates over the different regions is similar as in 1995 [10]. For all but three regions the confidence interval contains the countries average in both years. Applying the average of 3.9 and 4.4 per 1000 to these regions will only result in approximately 25 reports more. For Den Haag the downward trend has stopped and seems to be random variation. Overall the more even distribution for the past three years is regarded as a sign of diminished underreporting.
Lowest rates seems to be from area's where Child Health Care is less professionalised and GP's have clinics for their own patients. Some regional variation of reporting rate is acceptable because "soft" criteria as need for consultation and advice and parental apprehension play a role in reporting. The wide reporting criteria are however a tool against underreporting and are helpful in detecting new and rare side effects.

7.3.3 Type of Events

Whether underreporting is evenly distributed over the different event categories is hard to decide, since background rates are lacking for most events. And prospective studies about adverse events are usually too small in numbers to detect rare events. Moreover the lack of controls without any vaccination does not allow accurate attributive risk measurements/computing.

For febrile convulsions a recent prospective study in the Netherlands disclosed 1 febrile convulsion after MMR (and none after DPTP), mounting up to approximately 1 in 10000 children [17]. The number of febrile convulsions following the fourth DPTP and MMR1 seems to be compatible with this Figure.
For collapse after DPTP vaccinations only two small prospective studies were done with incidence rates of 1:1750 and 1:2780 [17-19]. In 1996 and 1997 120 and 145 Collapse reactions were reported, similar to the 134 and 137 in 1994 and 1995. This amounts to about 1 in 1500 children.
The relative frequencies are comparable also in 1994-1997. The increase in discoloured legs seems striking but must be interpreted with care, because in 1994 and before this was not considered a separate category, with application of case definitions. In 1995, 1996 and 1997 there were similar frequencies and distribution. See under Paragraph 7.8.2. We will report on discoloured legs separately.
For Idiopathic Thrombocytopenic Purpura (ITP) following MMR there seems to be consistent underreporting. According to the literature ITP may follow MMR in up to 1 in 23000 children [20,21]. Our reporting rate is 2-3 every year. Moreover most reports of ITP come in when the second MMR is due, some seven years later! Active surveillance with data linkage is planned as soon as PEA databases do include the exact vaccination date instead of month and year of vaccination. Hospital admission information on date and diagnosis must be accurate also however. ITP could also be included in the periodic sentinels among paediatricians, which may also reveal incidence rates of ITP in the Netherlands.

7.4 Age and Sex Distribution

The remarkable overrepresentation of reports following the first vaccinations reflects several different factors. First there is the young age of the children with the inherent apprehension of the parents. It is often the first time the child is (made) sick. But also there are several frequent age specific adverse reactions as well as age specific chance occurrences. As part of good professional standards, clinic staff asks for adverse events before administering the next dose of vaccines. It is for conceivable that there is also a certain degree of “getting used to” (common) reactions like fever, local inflammation and crying, with subsequent lower reporting rates as age progresses (higher dose numbers). DPTP is more reactogenic than MMR.
Like in previous years there is still some overrepresentation of boys in most categories, though a little less than in the years before. For collapse reaction and minor illness this is most consistent over the years. For most categories it is not possible to exclude selective reporting by sex, because of lack of background/incidence rates. Selective apprehension in parents may play a role however.

7.5 Diagnosis, Additional Information and Follow up

Verification and additional information with follow up is considered important in the monitoring of the safety of the vaccination programme. 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 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 talking 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.
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 in indications, contra-indications, vaccines or schedules as well as to certain 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.[22] See also Paragraph 7.8.1.

7.6 Causality Assessment

Assessing causal relation is regarded important in monitoring the safety of the vaccination programme. Not everything happening after vaccination is caused by the vaccination of course. Safety surveillance with causality assessment by RIVM and GR makes liberal reporting criteria possible and therefore more sensitive signal detecting. Careful causality assessment may free the programme from the burden of severe but unrelated adverse events as well as detect new or rare adverse reactions. 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.
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.

7.7 Specific Events

About half of the reports concern mild or moderate local or systemic symptoms. Quite often notification was because of the need for consultation. Especially skin symptoms seemed to cause uncertainty. In the history of the RVP no severe/life threatening allergic reactions have been reported; children usually receive further vaccination in normal clinic setting.
Experience for a number of years of uneventful MMR vaccination in children with chick egg white protein allergy, along with information of international studies, lead to adjustment of the procedures and the text of the package inserts [10,22].
The other half of the reported events were the so-called major events, not severe per se, but more a historical annotation of certain dramatic events. Hospital admission is not major automatically. In this respect reporting criteria differ from assessment criteria. Some specific events are discussed below.

7.7.1 Collapse

This well acknowledged adverse reaction is very frightening to parents. From 1993 onwards this reaction is no longer considered a contra-indication to further pertussis vaccinations [23,24].
Follow up has shown recurrence to be rare. In none of the 171 children (1994 and 1995 combined) with collapse reported after the first DPTP/Hib vaccinations collapse recurred after subsequent vaccinations (95% c.i. 0-2.1%)[22]. Recurrence does occur however, every year a few times. The pathophysiological mechanism has not been made clear, nor have risk factors been defined. A case-control study of collapse reactions reported in 1995 will be published separately. The total number of reported collapse reactions was in 1996 a little less than in 1994 and 1995 (134 and 137) and in 1997 a little more. Probably this is due to some chance variation. As in the two prior years strict case definitions have been applied. Several collapse reactions followed/coincided with (fierce crying of) discoloured legs syndrome (see below).

7.7.2 Discoloured Legs

From 1995 onwards, discoloured legs is considered a distinct event category. Case definitions are used. This assures a rather homogeneous event group and allows further systematic follow up and study of risk factors. Descriptive epidemiology will be reported on separately and a study of risk factors is being planned. Retrospect reviewing of reports before the

introduction of simultaneous Hib vaccination is on the way. The number and distribution of reports in 1995, 1996 and 1997 are similar.
Discoloured legs were initially reported as, anaphylactic shock, Henoch Schönlein disease, sepsis, meningitis, allergic reaction, convulsion and severe local reaction, among others. The distribution with predominantly reports after the first vaccinations does not suggest an allergic mechanism; moreover all children experiencing discoloured legs in 1995 were subsequently vaccinated. A few times discoloured legs recurred, not necessarily after the next vaccination, but no other untoward symptoms developed.

7.7.3 Idiopathic Thrombocytopenic Purpura

One and four cases of ITP were reported after MMR vaccination in 1996 and 1997 respectively. This is still considered to be an underreported event. Because of the apparent underreporting an active surveillance study is planned. We have not received a report of recurrence of ITP after the second dose of MMR, but numbers are small.

7.7.4 Diabetes Mellitus

No cases of Diabetes Mellitus were reported. Cases reported in the periodic sentinel studies of Dutch paediatricians (NSCK) are checked retrospectively on the timing of Hib and MMR vaccinations (in collaboration with TNO&PG) [25,26]. Evaluation showed that the increase in the incidence rate of DM started well before the introduction of Hib vaccinations in the Netherlands, and did not coincide with the start of routine Hib vaccinations as in other countries (where Hib vaccinations were included years earlier than in the Netherlands). Reappraisal of earlier studies in Finland showed the increase in DM incidence rate not to be associated with Hib vaccinations [27-30].

7.7.5 Death

Deaths were reported nine and three times respectively in 1996 and 1997; none were considered caused or potentiated by the vaccinations. The vaccination did not cause confusion or delay in the diagnosis as is known to occur sometimes. Because of bias by selective reporting an active surveillance project is considered, for the purpose of defining background rates, and time series analysis.

7.8 Prevention of Side Effects

Contra-indications are meant to prevent adverse reactions. They are the result of the balance of the risk of the target diseases, underlying disorders and the risk of vaccination.
Currently for DPTP no contra-indications are valid anymore. Individual adjustment of the schedule or precautions and special counselling of parents may be opted for, in special circumstances.

Of course good procedures of vaccine distribution and administration are of importance, including cold chain procurement and desinfection of the vials. Faulty procedures have not been implicated in any the reported adverse events this year again.
Excessive cooling of the injection site may increase local reactions. Fierce rubbing/massaging of the injection site straight after administration however may diminish local complaints and shorten crying because of distraction. Data are lacking of the effect on injection site symptoms of local/regional/individual procedures, like application of yoghurt, cabbage leaves, cucumber, menthol ointment and several homeopathic or herbal remedies. These procedures may have their own side effects!
Vaccinations under the RVP are routinely done in Child Health Clinic setting. Emergency sets of corticoids, epinephrine and antihistaminics are not available in accordance to the guidelines of the Inspectorate of Health Care. These sets have never been necessary so far and availability may lead to inadvertent use. Routine paracetamol prophylactic is advised against but sometimes prophylactic seems reasonable after severe complaints following prior vaccinations or in preventing fever in children with a history of febrile convulsions. Paracetamol may be used in case of excessive crying or severe pain. But fever should primarily be handled by cool clothing and cold sponging. It is most important that parents are advised to consult their GP in case of severe symptoms, so that concomitant disease will not be overlooked and (fatal) delay is avoided. However in case of clear-cut reactions like collapse or discoloured legs initial assessment suffices and one should not go through the whole ALTE protocol or allergic/neurological screening.
Attention should be paid not only to education of parents but also to education of GP’s and paediatricians in this respect. Vaccine adverse reactions should be included in the differential diagnosis, nothing more but nothing less either.
Deferral or discontinuation of vaccines or components because of adverse events should be considered an indirect side effect of vaccination and should be avoided. It should be stressed that serious adverse reactions are extremely rare and that lasting adverse effects if any are extremely rare. Vaccination in (outpatient) care in hospital may alleviate parental anxieties in rare instances, it is however not considered a medical necessity.

7.9 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 vaccination programme. The low threshold 24h-telephone service for reporting, consultation and advice is of great value for the current enhanced passive surveillance system. The quality of data generated by this system allows systematic follow up and study of specific adverse events. 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 studies.

For rare adverse events, like meningitis or ITP other strategies must be considered. Data linkage possibilities are being explored. A serious drawback is the lack of exact dates of vaccination in the PEA databases. Only four of the thirteen databases include lot numbers. Also the (adherence to) case definitions in hospital admission or discharge or mortality registers should be secured.
International collaboration on adverse event surveillance and studies should be expanded.
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.

8. Conclusions and Recommendations

In 1996 and 1997 the increase in reported adverse events seems to have levelled off. The regional distribution is satisfactorily, but there is no room for complacency. Febrile convulsions and collapse reactions seem to have a stable reporting rate, consistent with the incidence rate from prospective studies. 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.
Detailed study of epidemiology, sequelae, follow up and risk factors should be performed regarding some specific adverse events.
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 should 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.
Active surveillance of adverse events, through sentinel study and data linkage is planned in addition to the passive surveillance. Possibilities for study of extremely rare severe events and long term effects are being explored. 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 1998 and 1999
- 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
- active study of tolerability of DPTP/Hib vaccinations also in relation to the younger age schedule.

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 732 and 822 reports must be regarded in relation to a total of more than 2 million vaccines administered and of 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 1996 + 1997

STAATSTOEZICHT
OP DE VOLKSGEZONDHEID

Inspectie voor de Gezondheidszorg

VACCINATIEPROGRAMMA 1996

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

1996	1995	1992	1987
DKTP + Hib	DKTP + Hib + BMR	DTP	DTP + BMR

ZUIGELINGEN en KLEUTERS

VACCINATIESCHEMA

- DKTP (Difterie - Kinkhoest - Tetanus - Poliomyelitis)

  Op de leeftijd van respectievelijk 3, 4 en 5 maanden wordt één DKTP-injectie gegeven. 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 Nederlands Tijdschrift voor Geneeskunde 1989; 133, nr. 40, blz. 1975-1977) en in plaats van DKTP, DTP wordt gegeven, dient degene die de enting verricht dit **duidelijk** te vermelden op de oproepkaart, die naar de entadministratie wordt gezonden.

- Hib (Haemophilus influenzae type b)

  Op de leeftijd van respectievelijk 3, 4 en 5 maanden wordt één Hib-injectie gegeven. De vierde Hib-injectie wordt tenminste zes maanden na de derde Hib-injectie gegeven.
  Alleen kinderen geboren vanaf 1 april 1993 komen in het kader van het vaccinatieprogramma voor deze vaccinatie in aanmerking.
  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 1992 geboren kinderen worden in 1996 gerevaccineerd met DTP- vaccin. Afhankelijk van de reeds vroeger gegeven entingen worden 1, 2 of 3 injecties gegeven (zie Nederlands Tijdschrift voor Geneeskunde 1987; 131 nr. 15, blz. 641).
Dosering: 1 ml INTRAMUSCULAIR.

2. SCHOOLKINDEREN

VACCINATIESCHEMA

De in 1987 geboren kinderen worden in 1996 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 1987 geboren kinderen krijgen in 1996 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 Entadministrateurs.

PROVINCIE	ADRES	TELEFOON	FAX
GRONINGEN	Gorechtkade 8, 9713 CA Groningen	050-3686350	050-3138404
FRIESLAND	Sixmastraat 2, 8932 PA Leeuwarden	058-2890555	058-2880286
DRENTHE	Lauwers 9, 9405 BL Assen	0592-395260	0592-354224
OVERIJSSEL	Strangeweg 25, 7731 GV Ommen	0529-455717	0529-455805
FLEVOLAND	Strangeweg 25, 7731 GV Ommen	0529-455717	0529-455805
GELDERLAND	Korte Coehoornstraat 2, 6811 LB Arnhem	026-4429242	026-4434999
UTRECHT	Zoutkamperschans 7, 3432 TZ Nieuwegein	030-6881376	030-6881517
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	010-4339237
ZEELAND	Magnolia 55, 4461 EV Goes	0113-249246	0113-249240
NRD-BRABANT	Bosscheweg 57, 5056 KA Berkel-Enschot	013-5384849	013-5384848
LIMBURG	Kleine Steeg 7, 6131 KJ Sittard	046-4596262	046-4529733

4. ALGEMEEN

4.1 ORGANISATIE.
De uitvoering van het vaccinatieprogramma wordt verzorgd door de plaatselijke entgemeenschappen (bestaande uit vertegenwoordigers van huisartsen, kruisorganisatie en gemeente) in samenwerking met de GGD'en, onder verantwoordelijkheid van de artsen van de entadministraties en onder supervisie van de Hoofdinspecteur en de Regionale Inspecteurs voor de Gezondheidszorg

4.2 VACCINDISTRIBUTIE.
De vaccins worden door de SVM (Stichting tot bevordering van de Volksgezondheid en Milieuhygiëne) afgeleverd aan de erkende depôts. De distributie vanuit deze 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.

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 Entadministraties.

4.7 Alle nadere regelingen welke met betrekking tot het vaccinatieprogramma 1996 worden getroffen, vereisen de goedkeuring van de Hoofdinspecteur en de Regionale Inspecteurs 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, wordt GEEN gratis vaccin 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 Milieuhygiëne (RIVM) te Bilthoven, onder vermelding van het partijnummer van het betreffende vaccin is dan ook dringend gewenst (tel. (030) 274 24 24)

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 1995

De Hoofdinspecteur voor de Preventieve en Curatieve Gezondheidszorg

G.H.A. Siemons, arts.

STAATSTOEZICHT
OP DE VOLKSGEZONDHEID

Inspectie voor de Gezondheidszorg

VACCINATIEPROGRAMMA 1997

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

1997	1996	1993	1988
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 oproepkaart, 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.
Alleen kinderen geboren vanaf 1 april 1993 komen in het kader van het vaccinatieprogramma voor deze vaccinatie in aanmerking.
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 1993 geboren kinderen worden in 1997 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 1988 geboren kinderen worden in 1997 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 1988 geboren kinderen krijgen in 1997 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 Entadministrateurs.

PROVINCIE	ADRES	TELEFOON	FAX
GRONINGEN	Gorechtkade 8, 9713 CA Groningen	050-3686350	050-3138404
FRIESLAND	Sixmastraat 2, 8932 PA Leeuwarden	058-2890555	058-2880286
DRENTHE	Lauwers 9, 9405 BL Assen	0592-395260	0592-354224
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	010-4339237
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 wordt verzorgd door de plaatselijke entgemeenschappen (bestaande uit vertegenwoordigers van huisartsen, kruisorganisatie en gemeente) in samenwerking met de GGD'en, onder verantwoordelijkheid van de artsen van de entadministraties en onder supervisie van de Hoofdinspecteur en de Regionale Inspecteurs voor de Gezondheidszorg

4.2 VACCINDISTRIBUTIE.
De vaccins worden door de SVM (Stichting tot bevordering van de Volksgezondheid en Milieuhygiëne) afgeleverd aan de erkende depôts. De distributie vanuit deze 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.

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 Entadministraties.

4.7 Alle nadere regelingen welke met betrekking tot het vaccinatieprogramma 1997 worden getroffen, vereisen de goedkeuring van de Hoofdinspecteur en de Regionale Inspecteurs 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, wordt GEEN gratis vaccin 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 Milieuhygiëne (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 1996

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

4001/1

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 reconstitutie-vloeistof:

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