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Adverse Events Following Immunisation under the National Vaccination Programme of The Netherlands
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P.E.Vermeer-de Bondt, C. Wesselo,
A. Dzaferagic, T.A.J. Phaff

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RIVM, P.O. Box 1, 3720 BA Bilthoven, telephone: 31 - 30 - 274 91 11; telefax: 31 - 30 - 274 29 71

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 2000 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 nearly 2.5 million vaccinations 1142 AEFI were submitted. Of these 1.6% (18) was unclassifiable because of missing information. In 79% (884) of the classifiable events a possible causal relation with vaccination was established and in 21% (240) the events were judged to be coincidental. Compared with 1998 there was a small rise in the number of notifications consistent with the larger birth cohort. The accelerated schedule did not seem to have much effect, apart from a small rise in reported collapse reactions.

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Abbreviations

AE	Adverse Event
AEFI	Adverse Event Following Immunisation (melding of postvaccinale gebeurtenis)
AMK	Advice center and social services for child abuse and neglect
AR	Adverse Reaction (bijwerking)
BCG	Bacille Calmette Guérin (vaccine)
BHS	Breath Holding Spell
BMR	Bof Mazelen Rodehond vaccin (MMR)
CB	Child Health Clinic (consultatiebureau)
CBS	Statistics Netherlands
CIE	Centre for Infectious diseases Epidemiology (of RIVM)
DM	Diabetes Mellitis
DKTP	Difterie Kinkhoest Tetanus Polio vaccin (DPTP)
DTP	Diphtheria, Tetanus, (inactivated) Polio (vaccine)
DPTP	Diphtheria, Tetanus, (whole cell) Pertussis, (inactivated) Polio (vaccine)
EPI	Expanded Programme on Immunisation
GGD	Municipal Public Health Department
GP	General Practitioner, Family physician (huisarts)
GR	Health Council (Gezondheidsraad)
HepB	Hepatitis B (vaccine)
HBIg	Hepatitis B Immunoglobulin
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HHE	Hypotonic Hyporesponsive Episode (collapse)
Hib	Haemophilus influenzae type b (vaccine)
IGZ	Inspectorate of Health Care
IPV	Inactivated Polio Vaccine
ITP	Idiopathic Thrombocytopaenic Purpura
JGZ	Child Health Care (jeugdgezondheidszorg)
LAREB	Netherlands Pharmacovigilance Foundation
LVO	Laboratory for Clinical Vaccine Research (of RIVM)
MAE	Medical Consultant of PEA
MMR	Measles Mumps Rubella vaccine
NSCK	Netherlands Sentinel Centre Paediatrics….
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

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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. 97% van de spontane meldingen komt telefonisch binnen, in hoofdzaak vanuit de Jeugdgezondheidszorg (78%). Nadere gegevens van anderen dan de melder, bijvoorbeeld van ouders, huisarts of ziekenhuis worden in circa 67% van de meldingen verkregen. Na aanvulling en verificatie volgt het stellen van een (werk)diagnose en causaliteitbeoordeling door artsen van het RIVM. De beoordeling wordt meestal (94%) telefonisch teruggerapporteerd naar de melder. Schriftelijk verslag, veelal van de ernstiger of gecompliceerdere beelden, wordt naar alle medisch betrokkenen gestuurd. Door aanpassing van de werkwijze is er hierin een afname in aantal geweest in 1996. Een speciale commissie van de GR herbeoordeelt door hen geselecteerde meldingen individueel en de geaggregeerde gegevens van het jaarrapport steekproefsgewijs tijdens een jaarlijks werkbezoek aan het RIVM. De GR adviseert de Minister van Volksgezondheid jaarlijks over de veiligheid van het RVP. Het RIVM jaarrapport bevat alle binnengekomen meldingen in een kalenderjaar. Dit is het zevende jaarrapport.

In 2000 zijn 1142 meldingen binnengekomen, betreffende 1088 kinderen, op een totaal van bijna 2,5 miljoen vaccinaties per jaar. 18 meldingen (1,6%) waren niet te beoordelen wegens het ontbreken van informatie. 79% (884) van de meldingen werd als bijwerking beoordeeld met een mogelijk, waarschijnlijk of zeker causaal verband. Een toevallige samenloop werd aangenomen in 21% (240) van de meldingen.

Van de milde, zogenaamde “minor”, algemene, huid- of lokale verschijnselen (499) werden 333 (68%) meldingen als mogelijke bijwerking uitgeboekt in 2000.

Verkleurde benen (in 1995 voor het eerst afgesplitst van de huidverschijnselen) werden 126 keer gemeld, met in op drie na alle gevallen een mogelijke causale relatie en twee maal niet te beoordelen.

Andere zogenaamde “major” postvaccinale gebeurtenissen (gerubriceerd onder convulsies, collaps, “ziek major”, lokaal major, persistent screaming en de sterfgevallen) werden 643 keer gemeld en in 87% (551) beoordeeld als mogelijke bijwerking. Collaps, waaronder ook atypische en onvolledige episodes, werd 221 maal gediagnosticeerd, met slechts in vier gevallen geen oorzakelijk verband en een keer niet te beoordelen. Daarnaast enkele keren Breath-Holding-Spells (5) en flauwvallen (13) in oudere kinderen. In 2000 werden 63, convulsies gemeld, waarvan vier afebriel, die in 50 gevallen (79%) als mogelijke bijwerking werden beoordeeld. De 42 atypische aanvallen hadden in 74% (31) een mogelijk causaal verband. Epilepsie (7) werd niet als bijwerking beoordeeld, maar als een coïncidentie. Persistent screaming (39) werd in op een na alle gevallen gezien als bijwerking. Koorts van $\geq$40,5°C was de werkdiagnose bij 46 kinderen uit de “ziek major” groep, op drie na allemaal beschouwd als bijwerking. Van de 60 andere beelden uit de “ziek major” groep was er 16

keer een mogelijk causaal verband, heftig huilen/geprikkeld gedrag (3), vaccinitis (4), pallor (1), myoclonieën/rilling (1) en gastro-enteritis (1), in zes gevallen met ook zeer hoge koorts. Daarnaast was er in de “ziek major” groep nog ataxie (2), apneu (1), en ITP (2), en ontregeling van een stofwisselingsziekte (1). De overige 44 meldingen waren coïncidenteel. Er waren negen abcessen, waarvan geen kweken zijn gedaan, en acht anderszins heftige lokale reacties. De drie sterfgevallen in 2000 gemeld, zijn na uitgebreide evaluatie twee keer als toevallige samenloop beoordeeld, hoewel in geen van de gevallen een doodsoorzaak kon worden vastgesteld. Een kind is overleden na DKTP/Hib vaccinatie waarbij er mogelijk een (indirect) verband met de vaccinatie niet kon worden uitgesloten. Het betrof een kind met een ernstig aangeboren hartgebrek.
De meeste meldingen betroffen simultane DKTP en Hib vaccinaties (903). BMR was betrokken in 192 van de meldingen, waarvan 43 maal gecombineerd met andere vaccins. In 57% was er een mogelijke causale relatie met de BMR. Voor de andere vaccin(combinatie)s was dit percentage 87%.
Vergeleken met 1998 was er een stijging van het aantal meldingen van 3,8%. Dit past bij een groter geboorte cohort (3,6%). De vervroeging van het vaccinatieschema heeft mogelijk geleid tot meer (gemelde) collaps reacties, vooral na de eerste DKTP/Hib vaccinaties en ook bleekheid werd wat frequenter gemeld. Er is minder koorts en met koorts gepaard gaande beelden en ook minder huilgedrag gemeld dan in 1998 onder het oude schema. Voor het overige zijn geen belangrijke verschuivingen opgetreden. Er is over 2000 een zeer gelijkmatig meldpatroon over het land zonder significante verschillen per regio. Het totaal aantal mogelijke bijwerkingen moet in relatie gezien worden met het grote aantal verrichte vaccinaties. De grote gezondheidwinst die de vaccinaties van het RVP betekenen weegt op tegen de mogelijke bijwerkingen.

Summary

Adverse Events Following Immunisation (AEFI) under the Nationel Vaccination Programme (RVP) of the Netherlands 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. 97% of reports come in by telephone, in majority from Child health Clinic staff (78%). Parents, GP's and/or hospital provided additional data on request (67% of cases). After supplementation and verification of data RIVM makes a (working) diagnosis and assesses causality. The assessment is communicated to the reporting party usually by phone (94%). Written assessments, in case of more serious and complicated events, are sent to all medical professionals involved. A committee of GR reassesses the latter cases and the aggregated results of the other ones annually, and conducts cross checks during an audit visit. The GR advises the Minister of Health annually on the safety of the vaccination programme. RIVM reports fully, over all incoming reports in a calendar year since 1994. This is the seventh annual report.

In 2000, on a total of nearly 2.5 million vaccinations, 1142 AEFI were submitted, concerning 1088 children. Of these only 1.6% (18) were not classifiable because of missing information. 79% (884) of classifiable events were judged to be possibly, probably or definitely causally related with the vaccination and 21% (240) of the events were coincidental.

So-called "minor" skin, local or systemic events were registered in 499 cases of which 333 (68%) were classified as possible adverse reactions in 2000.

Discoloured legs were reported 126 times with a causal relation more or less likely in all but three cases and in two cases the vent was not classifiable. Other so-called "major" adverse events (categorised under convulsions, collapse, persistent screaming, general major illness and death) occurred in 643 cases of which 87% (551) were possible adverse reactions.

Collapse, including atypical and incomplete episodes, was diagnosed 221 times, in only four cases without causal relation and once non-classifiable. Five times breath holding spells and 13 times fainting in older children were reported. Convulsions were diagnosed in 63 cases, of which four were non-febrile, with in 79% (50) inferred causality. Atypical attacks were diagnosed 42 times, of which 74% (31) with a possible causal relation. Epilepsy (7) was not considered causally related with the vaccinations. All but one of the 39 persistent screaming cases were considered adverse reaction.

Fever $\geq$40.5°C was the working diagnosis in 46 cases of the major illness group, in all but three with inferred causality. Of the other 60 major illness cases 16 had a possible causal relation: fierce crying (3), "vaccinitis" (4), myoclonics/chills (1), pallor (1), and gastric-enteritis (1), in six cases with very high fever. Also ataxia (2), ITP (2), apnoea (1) and derangement of metabolic disorder (1) occurred. The other 44 were considered to be unrelated. There were nine abscesses, without cultures taken, and eight other major local reactions. In 2000, after thorough assessment, all three of the reported deaths were considered

chance occurrences with no definite other causes assessed however. In one case the child died after DPTP/Hib vaccination and a possible indirect influence of the vaccine could not be ruled out. This child had a severe inoperable congenital heart malformation.
Most frequently reports involved DPTP and Hib vaccination (903). MMR was involved 192 times, 43 times with simultaneous other vaccines. In 57% of cases there was a possible causal relation with MMR. For the other vaccine combinations this percentage was 87%. Compared to 1998 the number of reports rose with 3.8%. This is in line with the larger birth cohort (3.6%). The accelerated schedule possibly has lead to an increase in (reported) collapse reactions, especially after the first DPTP/Hib vaccinations. Also more episodes of pallor were reported, with a decrease in reported fever related event and crying episodes. In 2000 there was an extremely even reporting rate over the different regions in which none differed significantly from the country's average. The total of 1142 reports should be weighted against the large number of vaccines administered. The risk balance greatly favours the continuation of the vaccination programme.

1. Introduction

Identification, registration, and assessment of adverse events following drug-use are important aspects of post marketing research. Safety surveillance is even more important in the programmatic use of preventive strategies and intervention, especially when young children are involved. In The Netherlands the National Institute of Public Health and Environment (RIVM) has the task of monitoring adverse events following immunisations (AEFI) under the National Vaccination Programme (RVP). Already in 1962, with the introduction of the combined Diphtheria, Tetanus, whole-cell Pertussis and inactivated Polio vaccine (DPTP), a passive surveillance system has been adopted. Since 1984 the safety of the RVP is evaluated in close collaboration with the Health Council (GR). The annual reports of GR limit themselves to advising the Minister of Health on the safety issue of the RVP. By their nature they do not permit comparing rates and nature of adverse events between different vaccines, schedules or vaccine lots. The introduction of a vaccine against Haemophilus influenzae type b (Hib) coincided with a change in the procedure of registration and assessment of AEFI by RIVM in 1993. The annual reports on adverse events by RIVM are based on the year of notification. They include all reported events, irrespective of severity of symptoms or causal relationship with the vaccination. Reported events are ordered by nature and severity of the symptoms and by causal relation. This 2000 report contains a description of the procedures for soliciting notifications, verification of symptoms, diagnosis according to case definitions, and causality assessment. Notifications were followed with special attention this year because in this year the new accelerated schedule was applicable for all infants.
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 and the possible effects of the change in schedule. This RIVM report on adverse events is only issued in English. It includes a detailed description of the background, organisation and procedures of the National Vaccination Programme and the embedding in the Child Health Care System (JGZ).

2. Post Marketing Surveillance

Post marketing surveillance (PMS) consists of all actions towards better knowledge and understanding of (adverse) effects of vaccines beyond the pre-registration research. This is particularly relevant for the identification of rare as well as late adverse reactions, as their rate of occurrence can only be estimated after vaccine use in large populations over a long time [1]. Insight in overdose consequences or use in special groups or circumstances and interactions can be gained only through PMS. Moreover actual field effectiveness of many or most vaccines and vaccination programmes can only be determined after use over a long time in unselected populations and circumstances. The surveillance of the RVP is a task of the National Institute of Public Health and Environment (RIVM): the safety surveillance by the Laboratory for Clinical Vaccine Research (LVO) and the surveillance of effectiveness the Centre for Infectious Disease Epidemiology (CIE) [2].

Requirements for post marketing surveillance of adverse reactions have been stipulated in Dutch and European guidelines and legislation [3,4]. The World Health Organisation (WHO) advises on monitoring of adverse events following immunisations against the target diseases of the Expanded Programme on Immunisation (EPI) and on implementation of safety surveillance in the monitoring of immunisation programmes [5]. The WHO keeps a register of adverse reactions as part of the global drug- monitoring programme [6]. Currently there are several international projects to achieve increased quality of safety surveillance and to establish a register specifically for vaccines and vaccination programmes.

Close evaluation of the safety of vaccines is of special importance for maintaining public confidence in the vaccination programme as well as maintaining motivation and confidence of the health care providers. With the successful prevention of the target diseases, the perceived side effects of vaccines gain in importance [7,8]. Not only true side effects but also events with only a temporal association with the vaccination may jeopardise uptake of the vaccination programme [9]. This has been exemplified in Sweden, in the United Kingdom and in Japan in the seventies and eighties. Commotion about assumed neurological side effects caused a steep decline in vaccination coverage of pertussis vaccine and resulted in a subsequent rise of pertussis incidence with dozens of deaths and hundreds of children with severe and lasting sequelae of pertussis infection [10]. But also recently anxiety about safety rather than actual associations caused cessation of the hepatitis B programme in France [11,12]. Even at this moment the uptake of MMR in the UK is very much under pressure because of unfounded allegations about association of the vaccine with autism and inflammatory bowel disease [7,13,14,15,16,17,18,19,20].

To counteract similar (unfounded) disquiet in The Netherlands, RIVM has looked for a broader framework of safety surveillance, with a more scientific approach and independent reassessment. This led to the installation of a permanent committee of the Health Council (GR) in 1984. This committee reassesses the more serious events presented by RIVM. The GR advises the Minister of Health on the safety of the Vaccination Programme with annual reports [21]. Since the GR reports have no direct reference to year of notification or vaccination

and contain a selection of reported adverse events they cannot be used for analysis of trends or patterns in reporting of events nor for comparison of vaccines, lots or schedules. The annual reports of RIVM on adverse events aim to contribute to these goals, however, and may lead to specific follow up and systematic study of selected adverse events [22,23,24,25,26,27]. We hope this will lead to better understanding of pathogenesis and risk factors of specific adverse reactions. In turn, this may lead to changes in the vaccine or vaccination procedures or schedules and adjustment of precautions and contra-indications and improved management of adverse events.

3. The Netherlands Vaccination Programme

3.1 Vaccines and Schedule

In The Netherlands mass vaccinations of children were undertaken from 1952 onwards, with institution of the National Vaccination Programme (RVP) in 1957. From the start all vaccinations covered, were free of charge and have never been mandatory. Although a law existed on smallpox vaccinations, this law has never been enforced. With the eradication of smallpox vaccinations were abandoned and this law was revoked in 1978 [28,29]. At first mono-vaccines against diphtheria, tetanus and pertussis were used and the combined DTP vaccine since 1957. After the polio epidemic in 1956, vaccination against poliomyelitis was added. From 1962 onwards the combined DPTP vaccine, with an enhanced polio component (1978), is in use for vaccination of infants and young children and DTP(olio) for revaccination of older children. Rubella vaccination for 11 year old girls was added in 1974 and measles vaccination for 14 months old children in 1976. In 1987 the combined measles, mumps and rubella (MMR) vaccine replaced the mono-vaccines in a two-dose schedule for all children (14 months and 9 years). Mid 1993 vaccination against (invasive) infection with Haemophilus influenzae type b (Hib) was added for children born after April 1st 1993. The actual RVP schedule of 1999 is included in box 1 (appendix 2).
From this year on the programme has an earlier start, at two months in stead of three. This was decided upon because of the resurgence of pertussis in the Netherlands in order two achieve protection as early as possible for the youngest, most vulnerable children. The aim is to have given all children the third dose at five months of age. It was shown that with the prior schedule about one quart of children had not finished their primary series before six months of age[30].

Box 1. Schedule of the National Vaccination Programme of the Netherlands in 2000

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

DPTP, DTP and MMR are produced by SVM/RIVM; Hib (PRP-T) vaccine is produced by SVM/Pasteur-Merieux (see appendix 3-7). BCG vaccination is not included in the RVP. Vaccination is offered only to children with higher risk of acquiring tuberculosis when travelling to or staying in countries with a high prevalence. Usually vaccination takes place in the second half-year of life [28]. Hepatitis B vaccination (HepB) is available for children of HBsAg positive mothers. This vaccination is given, following HBIg administration at birth, in a four dose schedule at the ages of 2, 3, 4 and 11 months during the regular Child Health Clinic visits, simultaneous with DPTP and Hib. In Amsterdam, with a higher prevalence of

HBV carriers, a different schedule and delivery system is operational. Children of refugees and those awaiting political asylum have an accelerated schedule [28].
From December 1997 onwards the combined DPTP vaccine contains a better-defined pertussis component with on average a higher potency in the mouse protection test.
Because of temporary reduced supply MMR from a different manufacturer has been used in the RVP in 1999 and 2000. See appendix 7.

3.2 Vaccine Distribution and Registration

Vaccines for the RVP are supplied by SVM/RIVM and are kept in depot at a regional level at the Provincial Immunisation Administration (PEA) [28,29]. The PEA is responsible for further distribution to the providers. It also has the task to implement and monitor cold chain procedures at the Child Health Clinics (CB) and Municipal Health Care Service (GGD). The Medical Consultant of the PEA (MAE) guards and promotes programme adherence.
The databases of the PEA contain name, sex, address and birth date of all children up till 13 years of age. The databases are linked with the municipal population registers and are updated regularly or on line, for birth, death and migration.
The PEA sends an invitation for vaccination, with a vaccination-registration document and information, to the parents of every child in the second month of life or after immigration. A bar coded card for every scheduled vaccine dose is included. These cards are to be returned to the PEA by the provider after the vaccine is administered. Duplicate cards are available at the vaccination settings. Returned cards are also used for reimbursement of the costs of vaccinating (approx. 5 Euro per vaccine) to the health care organisation. All administered vaccinations are entered in the databases of the PEA on an individual level; the PEA sends reminders to the child's address if necessary. The databases serve also the providers who can check the vaccination status of individual children, or of the population they serve. The data of the PEA follow the child when it moves from one place to another.
The PEA databases also contain results of heel prick tests and of prenatal hepatitis B screening and subsequent vaccinations.

3.3 Child Health Care System

The Child Health Care system (JGZ) aims to enrol all children living in the Netherlands. Child Health Care in the Netherlands is programmatic, following national guidelines with emphasis on age-specific items and uniform registration on the patient charts, up till the age of 18 years [31]. Up till four years of age (pre school) children attend the Child Health Clinic (CB) regularly. At school entry the Municipal Health Care Service (GGD) takes over. From then on the Child Health Care gets a more population based approach, with special attention to risk groups and fewer individual check-ups
The first contact with the family usually occurs less than a week after birth when a nurse visits the home for the heel prick test on phenylketonuria and congenital hypothyroidism (PKU/CHT). At a special home visit approximately two weeks after birth, parents get information on Child Health and an invitation for the first CB visit at one month of age. The nurse may make additional house calls.
In the first year of life about ten CB visits take place during which physical check-ups are

performed. These include full medical history and growth and developmental screening at appropriate ages and tests of vision and hearing. Weight, height and head circumferences are recorded on growth charts. Validated test forms are used for developmental follow up. Data on physical examination are also recorded in a standardised form. Parents get advice on food and supplements and information about behaviour, safety issues and upbringing. Intervals between visits gets larger as age increases, from four weeks to three months up till the age of 15 months and after that with increasing intervals of three, six and nine months up till the age of four years. The child is seen depending on age specific problems alternating by a nurse or a physician specially trained in Child Health. On individual basis this schedule may be adjusted, and the nurse may make house calls.
The RVP is fully embedded in the Child Health Care system and vaccinations are given during the routine visits. Good professional standards include asking explicitly after adverse events following vaccination at the next visit and before administration of the next dose. The four-year booster shot with DTP is usually given at the last CB visit, before school entrance. Booster vaccination with DTP and MMR at nine years of age is organised in mass vaccination settings, with a possibility for catch up till the age of 13 years. For refugees and asylum seekers the programme covers vaccination up till 19 years of age.
Attendance of Child Health Clinics is very high, up to 99% and vaccination coverage for DPTP and Hib is over 97% with a slightly lower uptake for MMR of 95% [32]. (Accurate numbers on birth cohorts 1999 and 2000 have not yet been made available by IGZ).

3.4 Safety Surveillance

Since 1962 an adverse event (AE) surveillance system for the National Vaccination Programme (RVP) has been in effect. It is an enhanced passive reporting system including a 24 hours telephone service. This service is also available for consultation and advice on vaccination matters like schedules, contra-indications and precautions. This permanent availability and easy accessibility of the surveillance system make the reporting channel both fast and direct. AE may also be reported by mail or fax.
The annually distributed vaccination programme (appendix 2) by the Inspectorate of Health Care (IGZ) encourages Health Care providers to report adverse events to LVO-RIVM, giving address, telephone number and fax number. These are also mentioned on the package inserts of the vaccines (appendix 3-6). Most municipal and regional Child Health organisations, which provide the vast majority of vaccinations, have explicit guidelines for notifying AE to LVO-RIVM. The countrywide used guideline book on the RVP with background, execution and procedures, contains a (LVO-RIVM written) chapter on possible side effects and gives ample information on notification procedures [28]. LVO-RIVM promotes reporting through information, education and publications, for instance by contributing to refresher courses for Child Health Clinic staff. Family physicians and paediatricians are informed at symposia and lately also during their training. Feedback to the reporter of AE and other involved professionals has been an important tool in keeping the reporting rate at high levels.
Severe symptoms irrespective of medical intervention and irrespective of assumed causality are to be reported. Furthermore peculiar, uncommon or unexpected events, and events that

give rise to apprehension in parents or, Health Care providers or may lead to adverse publicity. Events that lead to deferral or cessation of further vaccinations are considered as serious and therefore should be reported, too (see box 2).

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

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

All notifications are accepted, registered and assessed by LVO-RIVM, irrespective of nature and severity of symptoms, diagnoses or time interval. No discrimination is made for official reports or consultations regarding adverse events. After receipt of a notification, a physician of LVO-RIVM reviews the information. Data are verified and the need for additional information is established. Additional information may be obtained from clinic staff, parents, general practitioners and hospital. Also data from the PEA are collected. Upon verification of symptoms and completion of data a (working) diagnosis is made. Interval with the vaccination and duration of the event is established and causality assessed. The feedback includes a description of verified symptoms, diagnosis and causality assessment by LVO-RIVM, and advice on subsequent vaccinations. See for detailed description on procedures chapter 5.

Since 1984 The Health Council (GR) re-evaluates reported AE on the basis of formal detailed written assessments by LVO-RIVM. These written assessments include the more serious reported events. Criteria for selection of the cases to be presented to GR have been mutually accepted. The other reports are cross-checked sample wise by GR. Since 1994, for reasons specified in chapter 2, LVO-RIVM makes an annual report on adverse events and no longer reports indirectly via reports by GR. For further details see paragraph 5.7.

4. Materials

4.1 Post Vaccination Events

Events following immunisations do not necessarily have a causal relation with the vaccination and some have a temporal association only and are in fact merely coincidental [7,8,31]. Therefore the neutral term adverse event is used to describe potential side effects. In this report the word "notification" designates all adverse events reported to us. We accept and record all notified events; in general only events within 28 days of vaccination are regarded as potential side effects. For some disease entities a longer period seems reasonable.
Following are some definitions used in this report.

- Vaccine: immuno-biologic product meant for active immunisation against one or more diseases.
- Vaccination or inoculation: all activities necessary for vaccine administration.
- Post vaccination event or Adverse Events Following Immunisations (AEFI): neutral term for unwanted, undesirable, unfavourable or adverse symptoms within certain time limits after vaccination irrespective of causal relation.
- Side effects or adverse reaction: an adverse event with a presumed, supposed or assessed causal relation with the vaccination.

Adverse events are thus divided in coincidental events and genuine side effects. Side effects are further subdivided in vaccine or vaccination intrinsic reactions, vaccine or vaccination potentiated events, and side effects through programmatic errors (see box 3)[33,34].

Box 3. Origin / Subdivision of adverse events by mechanism

a- Vaccine or vaccination intrinsic reactions	are caused by vaccine constituents or by vaccination procedures; examples are fever, local inflammation and crying. Collapse reaction and persistent screaming, occur less frequently and these maybe due to a special susceptibility in certain children.
b- Vaccine or vaccination potentiated events	are brought about in children with a special predisposition or risk factor. For instance, febrile convulsions.
c- Programmatic errors	are due to faulty procedures; for example subcutaneous administration of absorbed vaccines or non-sterile materials. Also too deep administration of BCG leading to abscess.
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 following vaccinations

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

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

5. Methods

5.1 Analysis

The processing and evaluation of notifications of adverse events is directed by a standard operating procedure (SOP 12 N-GCP-08). A physician reviews every incoming notification. The data are verified and the need for additional information is determined. A (working) diagnosis is made on the basis of the signs and symptoms, with assessment of the severity, duration and time interval. Causality is assessed on the basis of the type of vaccine, time interval and presumed pathophysiological mechanism of symptoms and alternative or other plausible causes of the event. The reporter is informed about the likelihood of a causal relation between vaccination and event and given advice on subsequent vaccinations. A formal written assessment is made of severe events and usually also of “alarming” less severe events and sent to all involved physicians. Anonymised copies of these written assessments are sent to the medical consultant of the PEA (MAE). These documents constitute the main source materials for reassessment by the committee of the GR and their subsequent annual advice to the Minister of Health. For further details see the following paragraphs of this chapter.

5.2 Additional Information

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

5.3 Working Diagnosis

After verification and completion of data a diagnosis is made. If the symptoms do not fulfil the criteria for a specific diagnosis, a working diagnosis is made based on the most important symptoms. Also the severity of the event, the duration of the symptoms and the time interval with the vaccination are determined as precisely as possible. Case definitions are in use for the most common adverse events (see paragraph 5.5) and for other diagnoses current medical standards are used. In case of doubt, confusing information, or difficulty in interpretation, the case is discussed in the periodic clinical conference of the physicians of LVO-RIVM. Minor difficulties in assessment may lead to ad hoc consultations and discussions to arrive at consensus.

5.4 Causality Assessment

Once it is clear, what exactly happened and when, and predisposing factors and underlying disease and circumstances have been established, causality will be assessed [34]. This requires

adequate knowledge of epidemiology, child health, immunology, etiology and differential diagnoses in paediatrics.

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

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

The nature of the vaccine and its constituents determine which side effects it may have and after how much time. For different (nature of) side effects different time limits/risk time may be applied. Causal relation will then be appraised on the basis of a checklist, resulting in an indication of the probability/chance that the vaccine is indeed the cause of the event. This list is not (to be) used as an algorithm although there are rules and limits for each point of consideration (see box 5).
After establishing to what extent the vaccine or vaccination has contributed to the event, its causality will be classified under one of the five listed different categories (box 6).
Certain (conclusive, convincing, definite), if the vaccine is proven to be the cause or if other causes are ruled out definitely; there should be a high specificity of the symptoms and a fitting interval. *Probable* causal relation, if there are no signs of other causes, but a fitting interval and a satisfactory biologic plausibility of vaccine/vaccination as cause of the event. If, however, there are other possible causes or the time interval is only just outside of the acceptable limits or symptoms are rather unspecific the causal relation is classified as *possible*. If a certain, probable or possible causal relation is established, the event is classified as adverse reaction or side effect.
If causal relation is regarded as (highly) *improbable*, there is only a temporal relation or a definite other cause for the symptoms; the event is then regarded as coincidental. This category includes also events without any causal relation with the vaccination. If data are insufficient for a (working) diagnosis and causality assessment, the event is listed under *unclassifiable*.

Box 6. Criteria for causality categorisation of AEFI

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

Generally also is considered to what extend the vaccine or vaccination has contributed to the

event and how. This is especially important in case faulty procedures are involved. This may have implications for management of side effects or contraindications. See also paragraph 4.1 and box 3.
By design of the RVP most vaccinations contain multiple antigens and single mono-vaccines are rarely administered. Therefore, even in case of assumed causality, attribution of the adverse events to a specific vaccine component or antigen may be difficult if not impossible. Sometimes with simultaneous administration of a dead and a live vaccine, attribution may be possible because of the different time intervals involved.

5.5 Event Categories

After assessment, all adverse events are classified under one of the ten different categories listed and clarified below. Some categories are subdivided in minor and major according to the severity of symptoms. Discoloured legs are a separate category, from 1995 onwards, for the purpose of aggregated analysis. Formerly these events were either classified under skin symptoms or under local reactions (see also box 7). For classification case definitions are used.

- Local (inflammatory) symptoms: consist of inflammation symptoms and other signs around the injection sites which are classified as minor if they are not extensive and are of limited duration. Atypical or unusual mild or moderate symptoms at the injection site are included in this category. Inflammation that is very extensive or extremely prolonged will be listed under major-local reactions, as will also cases of abscess or erysipelas. If there are accompanying systemic symptoms, the event is only booked under this category if local symptoms prevail or are considered major.
- General illness: includes all events that cannot be specifically categorised. For instance fever, respiratory or gastric-intestinal symptoms, crying, irritability, change in sleeping pattern or feeding behaviour, upper airway symptoms, rash illness, etceteras, fall under this category. Mild or moderate symptoms are listed under minor general illness, severe symptoms under major general illness. Hospitalisation per se does not preclude uptake in the minor category. Fever of 40.5°C and over is listed, by consent, as major general illness, except if associated with febrile convulsion or as part of another specific event. Prolonged mild or moderate fever is considered minor illness.
- Persistent screaming: (sudden) screaming, non-consolable and lasting for three hours or more, without one of the other specific diagnostic groups being applicable.
- General skin symptoms: skin symptoms that are not general (rash) illness and not considered extensions of a local reaction fall in this category. Like exanthema or other rashes as erythema, urticaria, that are not restricted to the injection site. Also circumscript lesions distant from the injection site, are included and the harlequin syndrome is booked under skin symptoms as well. Also some mild common systemic symptoms may be present. Subdivision is made according to severity in minor and major if applicable.
- Discoloured legs: symptoms are diffuse or patchy discoloration of the legs and/or leg petechiae, with or without swelling. Extensive local reactions are not included.
- Faints: Collapse reactions (HHE), a sudden loss of consciousness, loss of muscle tone and

pallor, are included unless these symptoms are explicable as post-ictal state or part of another disease entity. If symptoms are incomplete or atypical this is added as an annotation. In collapse following fierce crying that suddenly stops with or without the clear-cut breath holding phase, annotation will be made also. In case of classical breath holding spell with no or very short white phase this event will be listed under faints as a separate group. Fainting in older children is also listed as a separate group within this category. Just pallor or apathy or prolonged sleeping or limpness is not considered collapse reaction.

- Fits: Convulsions are all episodes with tonic and/or clonic muscle spasms and loss of consciousness. There is discrimination by body temperature in non-febrile and febrile convulsions. If fever is ≥38.5°C it is booked as febrile convulsion unless the convulsion is symptomatic for meningitis or for other illness. Febrile seizures of more than 15 minutes or asymmetrical or recurring within 24 hours are complex as opposed to simple (classic). Definite epileptic phenomena are included in this category also. Unspecifiable atypical attacks are a separate group under fits. These are paroxysmal occurrences without the specific criteria for collapse or convulsions. Nocturnal myoclonics are not included, neither are episodes of irritability, jitteriness or chills; these are grouped under general illness.
- Encephalitis or Encephalopathy: children younger than 24 months with encephalopathy have an explicit or marked loss of consciousness for at least 24 hours which is not caused by intoxication and not explicable as post-ictal state. In children older than 24 months at least 2 of the 3 following criteria must be fulfilled:
  - distinct change in mental status as disorientation, delirium or psychosis not caused by drugs;
  - marked decrease in consciousness not caused by seizures or medication;
  - seizures with (long lasting) loss of consciousness;

  Also signs of increased intracranial pressure may be present. In encephalitis, apart from the symptoms of encephalopathy there are additional signs of inflammation as fever and elevated cell counts in the cerebrospinal fluid.
- Anaphylactic Shock: Circulatory disturbance with hypotension and life threatening hypoperfusion of vital organs. This reaction should be in close temporal relation with intake of an allergen and with type I allergic mechanism involved. There may be accompanying laryngeal oedema or bronchospasm. Urticaria or wheezing alone is not included.
- Death: all reported children who died following immunisation are included in this category and not under one of the other listed categories.

Box 7. Main event categories with subdivision according to severity

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

5.6 Recording, Filing and Feedback

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

Severe and otherwise important adverse events as peculiarity or public unrest are as a rule put down in a formal written assessment and sent as feedback to the notifying physician and other involved medical professionals. This is done to ascertain that everyone involved gets the same information and to make the assessment (procedure) transparent. This document is filled together with the other information on the case. Because of the increasing workload, a less time consuming but equally effective procedure is sought in dialogue with the GR committee. In time, computer generated forms may be used, including listed verified symptoms, diagnosis and causality assessment with added advice, for most notifications that now get a full written report. The full written reports will be reserved for selected cases to be

re-evaluated by the GR committee. A project has been started for a database application, which allows for both feedback and aggregated analysis (see paragraph 5.8).

5.7 Health Council

Since 1984 the Health Council (GR) advises the Minister of Health on the safety of the National Vaccination Programme. A permanent committee has been appointed. Currently this expert group includes specialists on the following (different) fields: paediatrics, child health care, public health, epidemiology, microbiology, neurology, immunology, pharmaco-vigilance, pathology, vaccinology. GR base their safety advice mainly on the re-evaluation of the formal written assessments by LVO-RIVM and other available information on the anonymised cases. Together with data from the international medical literature and the aggregated reports of all notifications assessed by LVO-RIVM, the final judgement on the safety of the programme is reached. Physicians of LVO-RIVM are advisory members of this GR committee. Annually, GR makes a working visit to LVO-RIVM to audit the proper procedures and the completeness of registration and the quality and consistence of assessments.
Summarised reassessments of the GR committee are published in annual GR reports to the Minister of Health. Included are the AEFI, which are reassessed in the working period of the committee. There is an inherent, considerable and variable lag time between notification and this reassessment. Because the LVO-RIVM annual reports include all reported cases in a calendar year of which selected ones are included in the GR reports under responsibility of the committee, there is inevitable overlap. Thus numbers should not be added up.
Because the workload of the committee had to be reduced and assessment criteria have been agreed upon, only a selection of listed events are reassessed from 1996 onwards, with review of summarised reports of the other events. For the year under report (1998) this change in procedure did have impact on the number of written reports by LVO-RIVM and reassessed cases by GR. The GR committee however, considered all the aggregated results and this current report will be commented upon in their combined evaluation over five years.

5.8 Annual Reports and Aggregated Analysis

The coded forms are used as data sheets for the annual reports. For 1998 all reported events have been coded by one of us (PEVdB), after reappraisal of the information. Grouped events were checked for maximum consistency. Samples of final diagnosis, causality and categorisation have been discussed in the training programme of new investigators. The development of a robust database is behind schedule; therefore the data for this report have been entered in a temporary database with limited possibilities. Trend analysis as planned and more in-depth evaluation will have to wait until the new system is installed.

5.9 Quality Assurance

Assessment of adverse events is directed by a standard operating procedure (12N-GCP-08). There has been an independent external inspection and the GR audit over the year 1998. This will be commented upon in the combined GR report over 1997-2001.

6. Results

6.1 Number of Reports

In 2000 LVO-RIVM received 1129 notifications of adverse events, on a total of over 2 million vaccinations (Birth cohort 1999 is 200,445 and 206,619 in 2000, CBS per January 2002). 13 Notifications were compound with two distinct adverse events concerning one vaccination date. This annual report thus contains 1142 reported adverse events.
These reports involve 1088 children. There were 40 children with multiple reports, of which one concerned three different vaccination dates and once one of the double reports was also compound. Multiple and compound reports are listed under the respective event categories. In 1998 and 1999 there were 26 and 44 multiple reports and nine and eight compound reports with a total of 1100 and 1197 reports respectively. As described in paragraph 4.2, notifications concerning more than one vaccination date with only mild or common symptoms were booked as single reports unless reported on different dates (table 1).

Table 1. Types of reports of notified AEFI in 2000

notifications	children	adverse events
single	1036	1036[b]
multiple	39[a]	79
compound	12	24
compound and multiple	1	3
total	1088	1142

[a] once triple report
[b] 25 times multiple reports in previous or following years

From 1994 onwards comparisons of numbers are valid because the criteria for recording have been consistent, criteria for events eligible for written assessments have changed however. The number of advised vaccines has not changed since mid 1993, but there have been changes in vaccines and schedule. The birth cohort has gradually increased by approximately 9% since 1996 (CBS) (see paragraph 6.3 on reporting rates)

Table 2. Number of reported AEFI per year

year of notification	written assessments[a]	total[b]
1984	91	310
1985	139	325
1986	197	350
1987	149	325
1988	143	390
1989	141	440
1990	128	375
1991	136	340
1992	147	440
1993	227	496
1994	276	712
1995	234	800
1996	141	732
1997	76	822
1998	48	1100
1999	74	1197
2000	65	1142

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

Even without exact counts of former years, it is clear that the number of reported events increased in 1994 and 1995 with levelling off in 1996 and 1997 (table 2). In 1998 there was a significant increase in the number of reports judged to be partly due to increased awareness and apprehension, further reduced underreporting and possibly to some increase in actual adverse reactions as well [25]. In 1999 there was again an increase in number of reports. This was to be expected because the change in schedule from march 1999 onwards resulted in a larger number of vaccinated infants of about one month cohort with for dose 1, 2 and 3 approximately an extra 50,000 DPTP/Hib vaccinations. Any change in the programme may give rise to increased apprehension and awareness, which might in turn lead to an increase in notifications also. There appears to be a gradual increase in the birth cohort also. (See report on 1998, 000001 004, and 1999, 000001 005 www.rivm.nl)
As in previous years the notification rate is not even over the months, range 65-127, with again the lowest rate in January and December.

6.2 Reporters

The first person to notify LVO-RIVM about an adverse event is the reporter. As in previous years the vast majority of reports were made by telephone (table 3). Only 34 notifications came by regular mail, most frequently as regionally used, special report forms and some as (hospital discharge) letter. Also some reports came in by E-mail (1) or fax (3). Over the last six years the number of written notifications fluctuates a little between 25 en 51. Reports from Child Health Clinics accounted for 78%.

Table 3. Source and reporting route of AEFI in 1994-2000

		1994	1995	1996	1997	1998	1999	2000	tel.	mail
Clinic staff*	Physician	474	548	466	547	678	722	687	668	19
	Nurse	78	102	116	142	219	221	199	194	5
Paediatrician		60	59	56	39	69	70	80	73	7
General Practitioner		25	13	26	20	35	34	28	28	-
School Health Service		15	18	17	10	31	27	37	37	-
District Consultant		9	18	11	16	15	16	5	3	2
Parent		25	34	35	40	52	91	97	95	2
Other		5	6	2	7	1	9	7#	4	3
Unknown		21	2	3	1	-	7	2	2	-
Total		712	800	732	822	1100	1197	1142	1104	38

* including staff of refugee clinics
\# medicinal product information service (1), AMK (1), homeopath (1), lareb (4)

The parents of 97 (8.5%) children reported directly themselves; mostly they were advised to do so by the clinic staff. This percentage of parent reports is again higher than in 1999 (7.6%) with in previous years fluctuation around 4.8%. Absolute numbers are increasing from 1994 onwards. The other notification sources were more or less stable. We failed to note the reporting source in 2 cases. See also paragraph 6.6 for information sources.

6.3 Regional Distribution

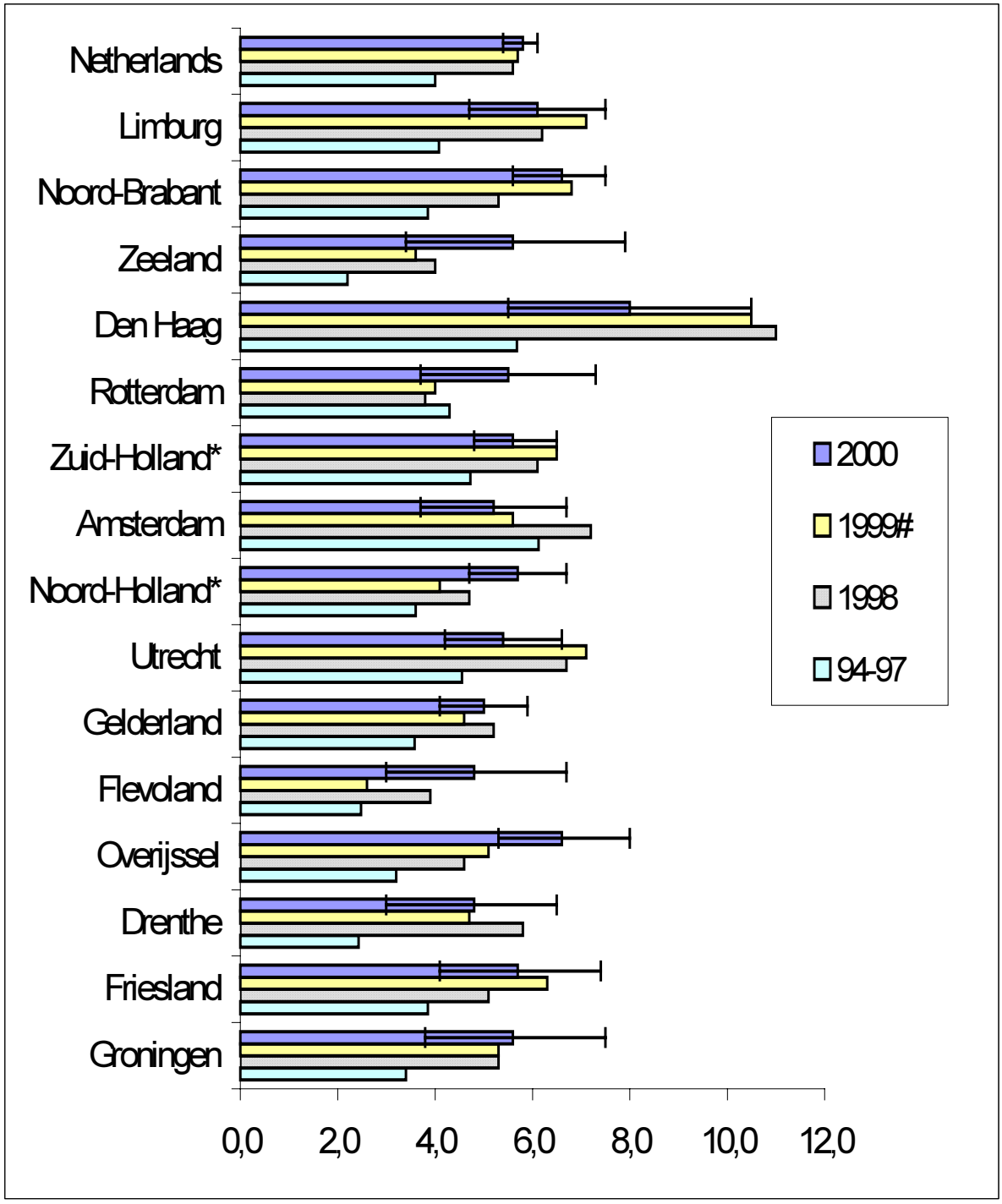
Reports come from all over the country, but are not evenly spread. Standardisation of the rate per 1000 vaccinated infants is done according to the data from the PEA[32]. In this report the rates for 1997 and 1998 have been adjusted since the coverage data for these respective years

have been made available by IGZ. Compared with the approximation in the previous reports there are only minor differences, with slightly lower rates for 1997 (4.3 in stead of 4.4) and for 1998 5.6 in stead of 5.9. The increase in rate in 1998 remains statistically significant however. The accurate data for 1999 and 2000 are not available yet therefore coverage data for 1998 have been used. For 1999 this new estimation was again adjusted with an approximation of the average increase of vaccinated infants per region caused by the change in schedule. Since the regular summarised reports of coverage data do not contain information on timing of the vaccination there will remain inevitable inaccuracies in estimated rates per region for this year. 1998 and 2000 will be more readily comparable, for trends and the effects of the accelerated schedule.
The birth cohort increased from a little below 190,000 in 1996 to 206,000 in 2000.
Comparing the different regions over 1998 and 2000 does show a small increase in rates, but the overall rates of 5.6 and 5.8 are not statistically significant and can well be caused by the somewhat larger birth cohort. We will comment upon differences in specific events in the respective paragraphs. For 2000 all confidence intervals for the rates per region contain the country's average, so reporting rates seem to be more evenly over the different regions than in former years (1999 not included for reasons specifies above) with 2-3 outliers per year.

Table 4. Regional distribution of reported AEFI in 1994-2000, per 1000 vaccinated infants[a]

	1994	1995	1996	95% c.i.	1997	95% c.i. [b]	1998	95% c.i. [b]	1999 [c]	95% c.i. [b]	2000[d]	95% c.i. [b]
Groningen	3.1	4.3	3.5	2.0-4.9	2.7	1.4-4.0	5.3	3.5-7.1	5,3	3.6-7.1	5.6	3.8-7.5
Friesland	2.5	4.7	3.6	2.2-5.0	4.6	3.1-6.1	5.1	3.5-6.7	6,3	4.6-8.0	5.7	4.1-7.4
Drenthe	1.8	2.0	3.2	1.7-4.7	2.7	1.3-4.1	5.8	3.9-7.7	4,7	3.0-6.4	4.8	3.0-6.5
Overijssel	2.1	4.0	2.7	1.8-3.5	4.0	3.0-5.1	4.6	3.5-5.8	5,1	3.9-6.2	6.6	5.3-8.0
Flevoland	1.4	3.4	2.6	1.2-4.1	2.5	1.1-3.9	3.9	2.2-5.8	2,6	1.2-3.9	4.8	3.0-6.7
Gelderland	2.9	4.0	3.5	2.7-4.3	3.9	3.1-4.7	5.2	4.3-6.2	4,6	3.7-5.4	5.0	4.1-5.9
Utrecht	4.6	4.2	4.4	3.3-5.5	5.0	3.8-6.4	6.7	5.4-8.0	7,1	5.7-8.4	5.4	4.2-6.6
Noord-Holland [e]	2.4	3.8	3.9	3.1-4.7	4.3	3.4-5.1	4.7	3.8-5.6	4,1	3.3-4.9	5.7	4.7-6.7
Amsterdam	8.2	6.0	4.4	2.9-5.8	5.9	4.3-7.5	7.2	5.5-9.0	5.6	4.1-7.1	5.2	3.7-6.7
Zuid-Holland [e]	4.6	5.0	4.5	3.7-5.2	4.8	4.0-5.6	6.1	5.2-7.0	6,5	5.6-7.4	5.6	4.8-6.5
Rotterdam	4.1	5.4	3.1	1.7-4.5	4.6	2.9-6.2	3.8	2.3-5.3	4.0	2.5-.5.5	5.5	3.7-7.3
Den Haag	6.0	3.0	7.3	4.8-9.7	6.4	4.2-8.6	11.0	8.1-14.0	10,5	7.7-13.2	8.0	5.5-10.5
Zeeland	1.2	2.5	2.2	0.8-3.6	2.9	1.3-4.5	4.0	2.1-5.9	3,6	1.8-5.3	5.6	3.4-7.9
Noord-Brabant	3.3	3.7	4.3	3.5-5.0	4.1	3.4-4.9	5.3	4.5-6.1	6,8	5.9-7.7	6.6	5.6-7.5
Limburg	3.4	4.2	3.4	2.3-4.4	5.3	4.0-6.6	6.2	4.8-7.5	7,1	5.6-8.5	6.1	4.7-7.5
Netherlands [f]	3.6	4.2	3.9	3.6-4.2	4.3	4.0-4.6	5.6	5.2-5.9	5.7	5.4-6.1	5.8	5.4-6.1

[a] for 1997 and 1998 figures have been adjusted because accurate coverage data have become available
[b] proportionate confidence interval
[c] for 1999 figures are adjusted with approximation of higher number of vaccinated infants because of change in schedule; 1998 coverage data have been used since the coverage data for 1999 have not yet been made available by IGZ
[d] coverage data of 1998 have been used because data for 2000 have not yet been published
[e] provinces without the three big cities (Amsterdam, Rotterdam, Den Haag)
[f] the Netherlands have a birth cohort of approximately 200.000 per year and vaccination coverage of 97% on average



\# for 1999 rates are based on birth cohort 1998 with approximation of increase in vaccinated infants because of the change in schedule to an earlier start.
for 1998 and before the published data on vaccinations per region are used.

* provinces without big cities Amsterdam, Rotterdam, Den Haag

Figure 1. Number of reported AEFI in 1994 till 2000 per 1000 vaccinated infants (with 95% confidence interval bars, proportional)

6.4 Vaccines

In 2000 most notifications were about recent vaccinations, all except 27. These latter notifications arose from concerns about planned booster vaccination or vaccination of younger siblings; in over one third of these cases parents called. The vaccine involved in these late reports was often MMR (16). One of the reports concerned adverse events in a previous generation, for vaccination (policy) of a new-born. All reports are included in the tables.

In table 5 scheduled vaccines and actually administered vaccines are listed. As in prior years, reports on the first DPTP/Hib dose were the most prevalent (418), with declining numbers on subsequent vaccinations and older age, respectively 191, 133, 166 for second, third and fourth dose. For actually simultaneous DPTP/Hib vaccinations (882) numbers were in between the numbers of 1998 (853) and 1999 (954) consistent with the larger number of vaccinated infants in 1999. For all other vaccines and combinations the numbers are similar to 1998. In 16 reports DPTP was given singly (22 and 20 in 1998 and 1999), without simultaneous other vaccines. Only one report concerned DPTP/Hib with simultaneous HepB vaccination. Six children received DTP(olio) instead of the scheduled DPTP by parental choice or fear because of prior adverse events (in siblings). The reason for DTP in the catch up schedule of the 2 year old refugee is not known.

Table 5. Schedule and vaccines of reported AEFI in 2000

vaccine given⇒ scheduled ⇓	dptp	dptp hib	hib	dptp hib mmr	dptp mmr	mmr	dtp	dtp mmr	dtp hib	dtp hib mmr	other	total 2000	1999	1998	1997	1996	1995
dptp1+hib1	6	406[a]	5	-	-	-	-	-	1	-	-	418	394	372	323	284	324
dptp2+hib2	3	186[b]	-	-	-	-	1	-	1	-	-	191	227	205	142	139	141
dptp3+hib3	-	131	2	-	-	-	-	-	-	-	-	133	166	148	103	96	103
dptp4+hib4	3[c]	155[d]	-	5[e]	1	-	1[f]	-	1[g]	-	-	166	188	148	95	88	83
dose?	2	4	-	-	-	-	-	-	-	-	-	6	8	14	7	4	9
mmr0	-	-	-	-	-	4	-	-	-	-	-	4	-	-	-	-	-
mmr1	-	-	-	-	-	141	-	-	-	-	-	141	139	139	98	80	95
dtp5	1[h]	-	-	-	-	-	31	-	-	1[i]	-	33	35	34	22	24	18
dtp6+mmr2	1[j]	-	-	-	-	4[k]	8[l]	36	-	-	-	49	33	33	25	13	21
hib catch-up	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	3
other	-	-	-	-	-	-	-	-	-	-	1[m]	1	6	7	7	4	3
total 2000	16	882	7	5	1	149	41	36	3	1	1	1142	1197	1100	822	732	800

[a] twice dptp1/hib2 and once dpt/opv/hib1 in foreign country
[b] once dptp2/hib1 and once dptp/hib plus hepb vaccine
[c] twice first and third catch up doses
[d] once unknown dose number with or without simultaneous hib
[e] twice before first birthday
[f] second catch up dose
[g] third catch up dose
[h] first catch up dose
[i] first catch up dose in refugee
[j] first catch up dose
[k] twice first dose and once test dose
[l] once with hepa vaccine with third dtp dose, twice catch up dose 2 and once dose 3, and once unknown dose number
[m] once vaccine not noted

In 2000 MMR was involved 192 times of which 149 concerned a single dose of MMR (four times before the age of one year and once an inadvertent second dose in a two yr old). Four children received a single MMR dose at school age, twice as catch up dose and once as a test-

dose. In six cases MMR was given with simultaneous DPTP with or without Hib, twice before the first birthday. 36 Times MMR was given simultaneous with DTP in the regular schedule at school age and once together with DTP and Hib in a catch up schedule in a two-year-old refugee.
DTP (booster) vaccination at 4 years (approx.) of age was involved 31 times, with another case a first catch up dose of DPTP vaccine at that age.
Reports concerned (re) vaccination at school age 49 times, of which four times only MMR , eight times only DTP (mainly catch up doses) once with hepA vaccine. Once child received a first catch up dose of DPTP.
Event categories are not equally distributed over the (scheduled) vaccinations (table 6). Faints, mainly collapse, and discoloured legs are most often reported after the first vaccinations, as is persistent screaming. This is consistent over the years. For these young-age specific adverse events numbers of reported collapse have gone up in 1999 but stabilised in 2000. The numbers of discoloured legs are stable over the last three years.
Convulsions, especially febrile, are reported more frequently after the fourth DPTP/Hib and the first MMR, than at younger ages.
No children with anaphylactic shock were reported and one case of (possible) encephalopathy/encephalitis after DTP5.
Compared to 1998, the year in which the old schedule still applied with start of the vaccinations at three months, there only seems an increase in faints, mainly collapse. All reported events are included in the numbers irrespective of causality. See for degree of causality paragraph 6.8, and also the specific events under paragraphs 6.9.
The age distribution over the different vaccines reflects the change in schedule as is illustrated in figures 4 and 5.

Table 6. Event category and (scheduled) vaccine dose of reported AEFI in 2000

vaccine⇒* / event ⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/hib?	mmr0	mmr1	dtp5	dtp6/mmr2	other	total 2000	1999	1998	1997	1996	1995
local reaction	9	12	5	25	2	1	3	5	13	-	75	89	69	49	46	39
general illness minor	120	53	45	57	1	1	53	13	23	-	366	373	405	254	244	280
major	18	11	14	24	1	1	33	4	-	-	106	111	85	57	51	55
persistent screaming	21	9	6	2	-	-	1	-	-	-	39	34	29	26	16	22
skin symptoms	16	25	4	6	1	1	13	2	6	1	75	85	75	74	58	61
discoloured legs	58	34	25	7	1	-	-	1	-	-	126	130	125	95	99	93
faints	155	41	22	8	-	-	-	6	7	-	239	244	174	155	134	147
fits	19	6	11	37	-	-	38	1	-	-	112	123	133	108	73	97
anaphylactic shock	-	-	-	-	-	-	-		-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	-	-	-	-	1	-	-	1	1	-	1	2	1
death	2	-	1	-	-	-	-		-	-	3	7	5	3	9	5
total	418	191	133	166	6	4	141	33	49	1	1142	1197	1100	822	732	800

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

The relative frequency of the different event categories is more or less the same over the years (figure 3). Minor illness stands out a little in 1998 and is a little above the range of the four previous years, but is again 31% for 1999 and 32% for 2000. For major illness, not

necessarily causally related, relative frequency goes up a little with 9.3% in 1999 and 2000. For fits and skin symptoms the relative frequency goes a little down perhaps.

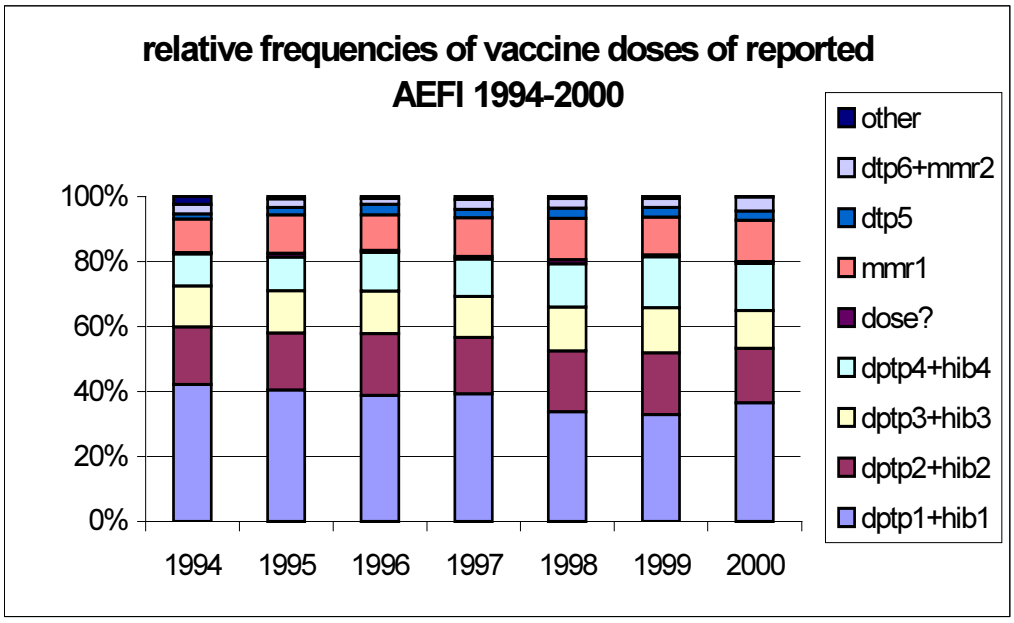


Figure 2. Relative frequencies of vaccine doses in reported AEFI in 1994-2000

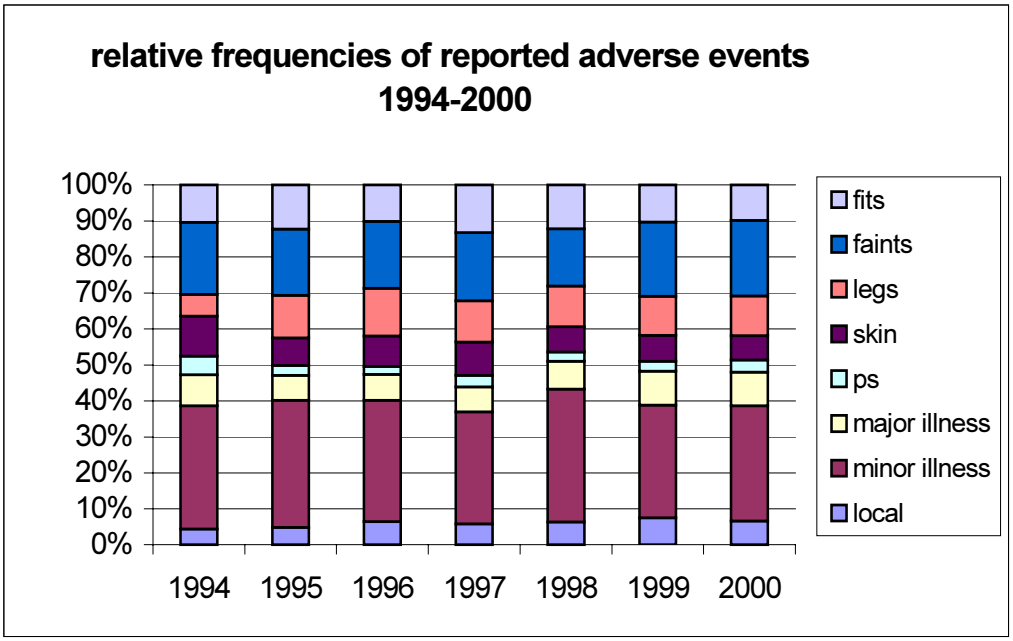


Figure 3. Relative frequencies of events in reported AEFI 1994-2000

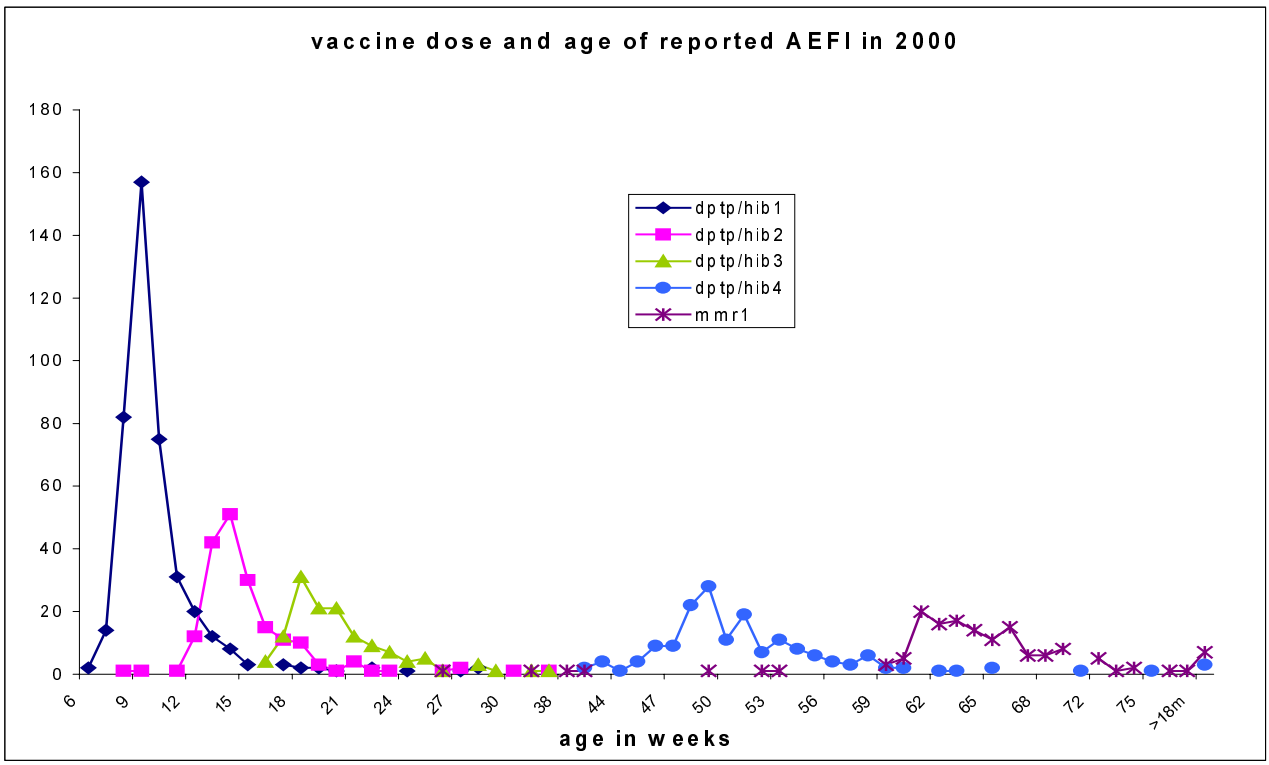


Figure 4. Age distribution of reported AEFI in 2000

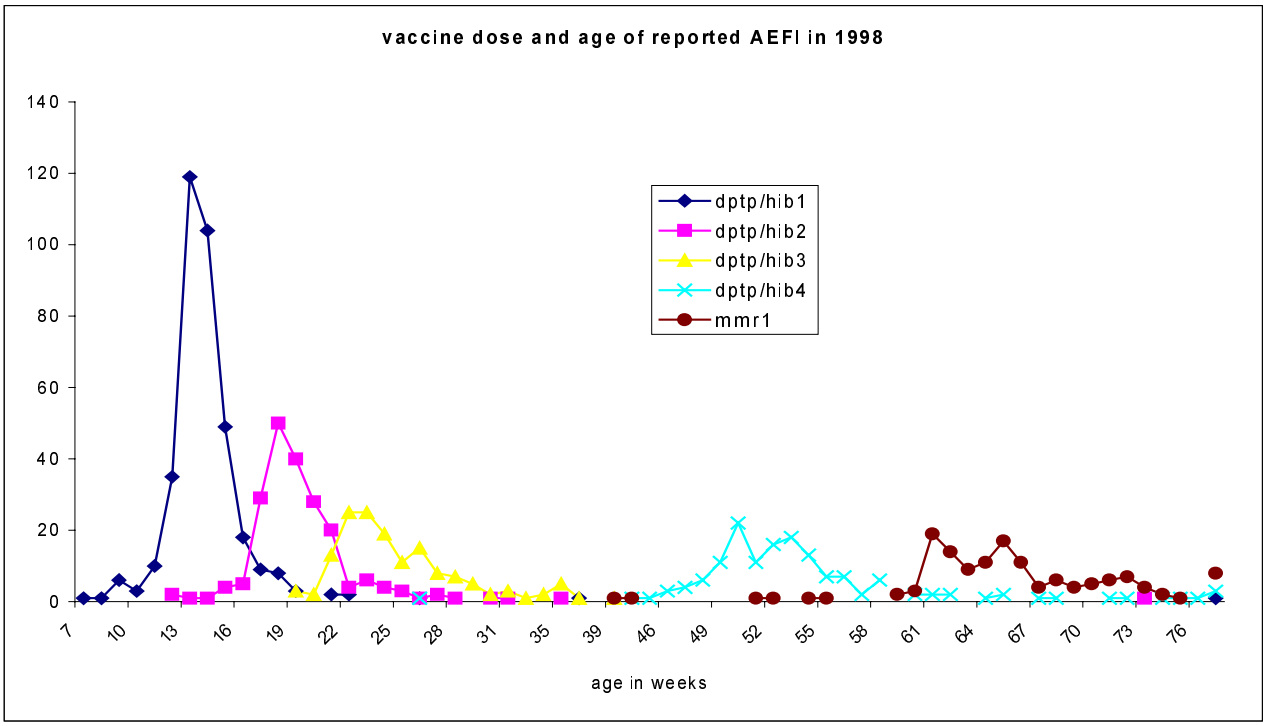


Figure 5. Age distribution of reported AEFI in 1998

6.5 Feedback to Reporters

Feedback of diagnosis and causality assessment with advice about further vaccinations is a major characteristic of the surveillance system. In about one third of the reports this is achieved in the notifying phone call. And in about another 15 percent final assessment did not change the preliminary evaluation substantially. The other half of the reports however could only be assessed after further verification and additional information. In over one third of notifications the original information lacked essential data. In about one third of the reports the notified diagnosis and/or involved vaccines or time intervals needed adjustment. The feedback, for these reports also, is increasingly done by telephone due to a change in procedures (in 1996). In 2000 6% of reports got a full written account, equal to 1999.

Table 7. Feedback method and events of reported AEFI in 1997-2000

event ⇓ feedback method⇒		written	tel.	1997 total	written	tel.	1998 total	written	tel.	1999 total	written	tel.	2000 total
local reaction		-	49	49	-	69	69	-	89	89	3	72	75
general illness	minor	3	251	254	4	401	405	5	368	373	8	358	366
	major	16	41	57	14	71	85	21	90	111	18	88	106
persistent screaming		-	26	26	-	29	29	-	34	34	-	39	39
skin symptoms		4	70	74	1	74	75	2	83	85	-	75	75
discoloured legs		4	91	95	1	124	125	9	121	130	5	121	126
faints		20	135	155	9	165	174	18	226	244	17	222	239
fits		25	83	108	14	119	133	11	112	123	15	97	112
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		1	-	1	-	-	-	1	-	1	1	-	1
death		3	-	3	5	-	5	7	-	7	3	-	3
total		76	746	822	48	1052	1100	74	1125	1197	70	1072	1142

6.6 Source of Information and Medical Intervention

In a little over one third of the notifications the reporter was the sole informant, in 67% information was received from others also, equal to 1998 and 1999 (table 8). In 94% the clinics (child health care, school health and refugee clinics) supplied information. Parents were in 66% (759) of cases contacted, some times during the notifying telephone call at the Child Health Clinic. This percentage is a little higher than in 1999 (63%) and parents were the sole informer of 41 reports (21 and 40 in 1998 and 1999). Hospital specialists supplied information in 18% of the reports, a little less than in 1999 (19%) and more than in 1997 and 1998 (15%).

The level of medical intervention sought or received may also illustrate the impact of adverse events. In 22% (256) of reported events no professional medical help was sought or was not reported to us or recorded by us and 12% of the parents (134) administered paracetamol suppositories or diazepam by rectiole for instance (in 1999 24% and 12% respectively). 66% of the parents contacted the clinic or GP, called the ambulance, or went to hospital, with 13 % admittance. In 1997, 1998 and 1999 these latter percentages were 52%, 60% and 64% with 11%, 10 % and 12% for admittance respectively. In table 9 intervention is ordered according to highest level used.

Table 8. Information sources and events of reported AEFI 2000

info ⇒	clinic*	+	+	+	+	+	+	+	+	-	-	-	-	-	-	1072
	parent	-	+	+	+	+	-	-	-	+	+	-	-	-	-	759
	gen. pract.	-	-	-	+	+	-	+	+	-	-	+	-	-	-	42
	hospital	-	-	+	-	+	+	-	+	+	-	-	+	-	-	207
	other	-	-	-	-	-	-	-	-	-	-	-	-	+	-	5
event ⇓	unknown	-	-	-	-	-	-	-	-	-	-	-	-	-	+	2
local reaction		30	30	1	2	1	1	1	-	-	4	1	3	1	-	75
general illness	minor	135	170	17	3	-	5	1	1	-	24	5	4	1	-	366
	major	31	38	19	1	2	9	-	1	1	2	-	1	1	-	106
persistent screaming		9	24	2	-	-	3	-	-	-	-	-	1	-	-	39
skin symptoms		27	28	4	1	1	5	3	-	-	2	1	1	1	1	75
discoloured legs		20	95	8	1	-	-	-	-	-	1	1	-	-	-	126
faints		31	139	44	3	-	12	1	2	-	6	-	1	-	-	239
fits		9	42	34	2	3	14	2	-	-	2	-	2	1	1	112
anaphylactic shock		-	-	-	-	1	-	-	-	-	-	-	-	-	-	-
encephalopathy/-it is		-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
death		-	-	1	-	-	1	-	1	-	-	-	-	-	-	3
total		292	566	130	13	8	50	8	5	1	41	8	13	5	2	1142

* child health , school health and refugee clinic

Table 9. Medical intervention and events of reported AEFI in 2000

intervention⇒ / event⇓		?	none[a]	supp[b]	clinic[c]	gp tel[d]	gp visit[e]	ambu lance[f]	out-patient	emerg ency	hospital stay	other[g]	post mortem	total
local reaction		18	6	2	15	5	18	-	7	3	1	-	-	75
general illness	minor	65	41	41	47	22	77	1	27	2	13	30	-	366
	major	8	2	11	3	5	27	-	10	1	32	7	-	106
persistent screaming		4	4	17	-	2	6	-	3	-	2	1	-	39
skin symptoms		15	2	3	8	1	29	-	10	-	2	5	-	75
discoloured legs		20	16	26	13	12	25	1	9	1	3	-	-	126
faints		18	23	23	16	22	55	4	11	10	56	1	-	239
fits		8	5	11	1	11	12	4	10	7	43	-	-	112
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		-	-	-	-	-	-	-	-	-	1	-	-	1
death		-	1	-	-	-	1	-	-	-	-	-	1	3
total 2000		156	100	134	103	80	250	10	87	24	153	44	1	1142

[a] homeopathic or herb remedies, baby massage or lemon socks are included in this group, as are cool sponging
[b] apart from paracetamol suppositories, stesolid rectioles and other prescribed or over the counter drugs are included
[c] telephone call or special visit to the clinic
[d] consultation of general practitioner by telephone
[e] examination by general practitioner
[f] ambulance call and home visit without subsequent transport to hospital
[g] mainly homeopaths

6.7 Sex Distribution

Overall more boys (54%) were reported than girls, similar to 1998 and 1999. In 1994 en before reports concerned boys in 60% of cases, with a gradual decrease from 1995 to 1998. (table 10). Distribution over the different events ranged from 47% (convulsions and local reactions) to 60% boys (minor illness) with events with less than 40 reports excluded. See for specifics on the events and subdivision, the respective categories under paragraph 6.9.

Table 10. Events and sex of reported AEFI in 1998 - 2000

event ⇓		sex⇒	male	female	unknown	1998 total	male	female	unknown	1999 total	male	female	unknown	2000 total
local reaction			33	31	5	69	44	42	3	89	34	39	2	75
general illness		minor	209	185	11	405	201	159	13	373	205	153	8	366
		major	49	36	-	85	58	53	-	111	63	42	1	106
persistent screaming			19	10	-	29	19	14	1	34	21	18	-	39
skin symptoms			40	29	6	75	50	34	1	85	36	35	4	75
discoloured legs			69	55	1	125	70	58	2	130	65	60	1	126
faints	collapse		80	77	1	158	119	102	-	221	124	97	-	221
	BHS		2	2	-	4	-	5	-	5	3	2	-	5
	fainting		6	5	1	12	9	8	1	18	4	8	1	13
fits	convulsions		34	31		65	37	38	2	77	27	35	1	63
	epilepsy		1	2	-	3	1	2	-	3	1	6	-	7
	atypical attacks		37	28	-	65	23	20	-	43	25	17	-	42
anaphylactic shock			-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis			-	-	-	-	-	1	-	1	1	-	-	1
death			2	3	-	5	6	1	-	7	2	1	-	3
total			581	494	25	1100	637	537	23	1197	611	513	18	1142

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

6.8 Causal Relation

Adverse reactions are events with (likelihood of) causality assessed as certain, probable or possible. In 2000, 79% of reports were considered adverse reactions, a little lower than in 1999 (84%) and 1998 (80%) 1997 (80%) and excluding non-classifiable events. The other events were considered coincidental events with improbable or absent causal relation with the vaccinations. 18 Notifications were not classifiable (1.6%).

Table 11. Causality and events of reported AEFI in 2000

event ⇓		causality⇒	certain	probable	possible	improbable	non classifiable	total	(% AR)*
local reaction			49	16	9	1	-	75	(99)
general illness		minor	-	140	102	118	6	366	(67)
		major	-	18	41	43	4	106	(58)
persistent screaming			-	28	10	1	-	39	(97)
skin symptoms			-	6	23	38	3	75	(47)
discoloured legs			-	106	15	3	2	126	(98)
faints	collapse		-	203	13	4	1	221	(98)
	BHS		-	5	-	-	-	5	(100)
	fainting		-	13	-	-	-	13	(100)
fits	convulsions		-	25	25	12	1	63	(81)
	epilepsy		-	-	-	7	-	7	(0)
	atypical attacks		-	11	20	11	-	42	(74)
anaphylactic shock			-	-	-	-	-	-	-
encephalopathy/-itis			-	-	-	1	-	1	(0)
death			-	-	1	1	1	3	(50)
total			49	571	264	240	18	1142	(79)

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

There are great differences in causality between the different event categories, but over the years very consistent. See for description and more detail the specific paragraphs under 6.9 and discussion in chapter 7. For MMR vaccination 57% of the 192 reported adverse events

were considered an adverse reaction in 2000. This was lower than in 1999 (69%) and higher than in 1998 and 1997 (50% and 53%). For DTP, DPTP and Hib vaccinations this percentage was 87%; for 1997, 1998 and 1999 this was 80%, 88% and 85% respectively.

6.9 Categories of Adverse Events

Classification into disease groups or event categories is done after full assessment of the reported event. Some disease groups stay "empty" because no events were reported in 1999.

6.9.1 Local reactions

In 2000, 75 predominant local reactions were reported in approximately equal frequencies after DPTP/Hib or DTP vaccinations (table 12). All but one reported local events were considered reactions (table 11).

Mostly (49) they were mild or moderate reactions of common inflammation with in 25 cases atypical symptoms, like some kind of local rash (7), possible infection (3), pigmentation (4), haematoma /fibrosis and/or dimpling (6), only swelling or itch (3). In five children signs of inflammation were mild or absent but there was marked reduction in use of the limp. This is booked separately as "avoidance behaviour". Symptoms were often one-sided, in majority DPTP site (10) but five times definitely both sided and three times Hib site. Once in children with simultaneous other vaccines the local reaction was definitely on the site of MMR. Once the BCG (4-6 weeks previously) probably caused one of the local reactions at the MMR site in a child with a single MMR vaccination. In about half the reports the site was not specified. Of the 17 children with so called major local reactions, six had extensive common inflammation and two had extreme "avoidance behaviour". Of the nine abscesses three were drained surgically and six drained spontaneously. Six times no cultures were taken and of the surgically drained we have no information about possible cultures. All abscesses were one sided, three times at the DPTP site, once at the Hib site and five times not specified. No faulty procedures were revealed.

Table 12. Local reactions and vaccines of reported AEFI in 2000

vaccine⇒ / event⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/hib?	mmr1	dtp5	dtp6/mmr2	total 2000	1999	1998	1997	1996
mild/moderate	2[a]	6	1	5	1	-	2	7[c]	24	28	32	28	20
severe/prolonged	-	-	1	6	-	-	2[b]	3[d]	12	11	6	8	7
abcess	4	2	1	2	-	-	-	-	9	11	9	-	4
atypical moderate	3	4	2	7	1	4	1	3	25	32	22	13	15
avoidance	-	-	-	5	-	-	-	-	5	7	nr	nr	nr
total	9	12	5	25	2	4	5	13	75	89	69	49	46

[a] once only Hib
[b] once dptp catch up dosis
[c] once mmr only test dosis and once dtp catch up only
[d] once dptp catch up only and once dtp catch up only

6.9.2 Systemic symptoms

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

minor general illness

In 366 children the complaints were considered minor illness in 2000, with in 33% improbable causal relation with the vaccination (in the four previous years 26-28%). See also table 11. Of all reports 75% concerned the scheduled DPTP/Hib vaccinations, most frequently events following the first DPTP/Hib, with the relative share slowly going down (table 13). For comparison the numbers of 1994-1999 are included.

Table 13. Minor illness and vaccines of reported AEFI in 1994-2000

scheduled vaccine ⇓	1994	1995	1996	1997	1998	1999	2000
dptp/hib1	104	102	85	100	117	102	120[a]
dptp/hib2	53	54	47	53	81	75	53[b]
dptp/hib3	37	46	34	42	60	58	45[c]
dptp/hib4	13	27	32	23	54	60[d]	55[d]
dptp/hib?	?	3	1	2	6	5	1[e]
dptp/hib/mmr1	?	2	3	1	-	2	2
mmr1	20	31	32	22	62	55	54[f]
dtp5	3	6	9	3	11	7	13
dtp6/mmr2	5	9	1	7	12	8	23[g]
other	7	-	-	1	2	1	-
total	242	280	244	254	405	373	366

[a] twice dptp only, three times hib only and once hib with dtp(ertussis) and opv in foreign country
[b] twice dptp only, once dptp/hib/hepb and once dtp catch up dose
[c] twice hib only
[d] twice dptp only, once dtp only and once dtp/hib
[e] once dptp only
[f] once mmr2 by mistake and once mmr0 before the first birthday
[g] twice dtp only and twice mmr only

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, 71, three times only sub-febrile temperature (37.5-<38.5°C). In all but 15 cases the fever was considered possibly causally related. Fever was also the most frequent symptom in the other diagnoses (161 times). Pallor and/or cyanosis was the second most frequent main symptom, 53 times, all judged to be causally related. Another 14 times pallor/cyanosis was an accompanying symptom. Crying was the main feature in 42 cases, 33 times vehement and seven times prolonged or unusually pitched; in four cases the crying had other causes. There often was pronounced crying in the other events also (48) or groaning (7). Irritability was quite frequently diagnosed (5), as were chills (10) and (sleeping) jerks or myoclonics (21), with or without fever, as often as main working diagnosis as in accompanying symptoms. Apathy or sleepiness was the main feature in 8 cases and gastric-intestinal complaints 15 times. Respiratory tract symptoms like common cold, tonsillitis, pseudocroup, pneumonia, otitis, asthma, bronchitis etceteras, were frequently diagnosed (34). In 2000 one child with red urine (myoglobinuria?) was reported and another child had hematuria repeatedly, indicative of renal disease. Of the 39 children with (possible) rash illness 17 were considered to be “vaccinitis” following MMR and of the other 22 all but two were judged to be coincidental events. See for further symptoms and causality table 14.

Table 14. Main (working) diagnosis or symptoms in minor illness of reported AEFI in 2000 (with number of adverse reactions)

symptom or diagnosis	1998	(AR*)	1999	(AR*)	2000	(AR*)	symptom or diagnosis	1998	(AR*)	1999	(AR*)	2000	(AR*)
fever	135	(118)	92	(83)	71	(56)	pallor and/or cyanosis	27	(27)	26	(26)	52	(53)
low temperature	-	-	1	(-)	1	(1)	jaundice.	-	-	1	(-)	-	-
crying	50	(47)	48	(46)	42	(38)	liverfunction abnormalities	-	-	1	(-)	-	-
groaning	-	-	1	(1)	1	(1)	rash (illness)	25	(2)	23	(3)	22	(2)
irritability	10	(7)	5	(5)	5	(2)	vaccinitis	9	(8)	21	(21)	17	(17)
meningismus	1	(-)	1	(1)	-	-	parotitis	3	(2)	3	(2)	5	(2)
myoclonics	16	(15)	25	(22)	21	(21)	swelling face/hands/feet/?	4	(2)	5	(5)	5	(4)
chills	13	(13)	10	(9)	10	(10)	lymphadenopathy	2	(1)	1	(-)	4	(2)
bulging fontanel	2	(-)	2	(2)	-	-	infectious disease	3	(-)	3	(-)	3	(-)
listlessness	1	(1)	1	(1)	5	(2)	allergy/atopy	1	(-)	3	(-)	2	(-)
drowsiness	3	(2)	3	(3)	4	(4)	feeding problems	6	(4)	3	(2)	4	(1)
prolonged sleep	8	(8)	1	(1)	4	(3)	vomiting	3	(2)	4	(4)	4	(1)
behavioural problem/-illness	5	(-)	10	(7)	10	(6)	diarrhoea	2	(-)	1	(1)	-	-
sleeping problems	-	-	-	-	5	(-)	stomatitis	-	-	-	-	1	(-)
neck pain/stiffness	2	(2)	-	-	-	-	gastro-enteritis	11	(4)	18	(7)	11	(3)
arthralgia/arthritis/coxitis	3	(2)	-	-	3	(1)	dehydration	1	(-)	-	-	-	-
hypertonia	-	-	1	(1)	1	(1)	obstipation/ belly ache	-	-	2	(-)	2	(-)
lying still/frozen	10	(8)	3	(2)	8	(8)	myoglobinuria?	4	(4)	2	(2)	-	-
limping/falling	3	(2)	-	-	-	-	urinary tract infection/hematuria	1	(-)	-	-	2	(-)
apnoea	1	(-)	1	(1)	1	(-)	epistaxis	1	(-)	-	-	1	(-)
low saturation	-	-	1	(1)	-	-	hyperventilation	-	-	2	(2)	2	(2)
asthma (attack)	2	(-)	2	(1)	4	(4)	whiplash	1	(1?)	-	-	-	-
airway infection	16	(-)	18	(-)	10	(-)	headache/migraine	2	(-)	-	-	-	-
cough	2	(-)	3	(-)	7	(2)	rolling eyes	1	(1)	4	(4)	1	(1)
dyspnea/wheezing	1	(-)	5	(4)	6	(-)	retardation	-	-	3	(-)	-	-
pseudocroup	1	(-)	2	(-)	2	(-)	nystagmus/abducens paralysis	1	(-)	1	(-)	1	(-)
tonsillitis/cold	1	(-)	1	(-)	1	(-)	transient episode undefinable	4	(1)	2	(2)	-	-
otitis	1	(-)	1	(-)	6	(-)	not specified	6	(2)	6	(1)	6	(-)

* adverse reactions

Of the reported AEFI 76 concerned MMR vaccine with in 37 cases a possible causal relation, of which ten times attributed to simultaneous DTP or DPTP/Hib. Three times the event was not classifiable. Thus in 36% of the reports of minor general illness following MMR the event was considered adverse reaction. For the other vaccine combinations this was the case in 70%, with three events not classifiable.

major general illness

In 2000, 106 reports were classified as major general illness, compared to 85 in 1998 and 111 in 1999 (table 15). The distribution is more even over the scheduled vaccines than in the minor illness group. For causality see table 16. Overall, 59 events were considered adverse reactions (58%, compared to 69% in 1998 and 1999). In the 43 AEFI considered to be chance occurrences the time interval was not plausible and/or other causes were established. Four reports were not classifiable or could not be substantiated. 34 Reports concerned MMR1 with in 13 cases (40%) assessed causality (43% in 1999). For the other vaccines or combinations 46 (66%) reported events were considered to be possible adverse reactions, compared to 75% in 1998 and 1999. See also table 16.

Very high fever (≥40.5°C) was the working diagnosis in 46 cases. In all but three cases causality was inferred. In the other events in this category very high fever was present in 14 cases, in all but three in the one-year-old children, and in 57% considered coincidental. In other event categories there was very high fever in another 14 cases, mainly in febrile convulsions.

Table 15. Major illness and vaccines of reported AEFI in 2000

diagnosis⇓ vaccine⇒	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/hib?	mmr1	dtp5	total
high fever	4	7	11	17	-	6	1	46
crying/irritability	2	-	1	-	-	-	-	3
pallor	-	1	-	-	-	-	-	1
arthritis/discitis	-	-	-	1	-	2	1	4
apnoea/respiratory insufficiency	1	-	-	-	-	-	-	1
guillain barre/flaccid paralysis	-	1	-	-	-	-	-	1
pneumonia/ bronchiolitis	3	-	-	-	-	1	-	4
rash illness	2	-	-	1	-	4	-	7
vaccinitis	-	-	-	-	-	4[b]	-	4
deafness	-	-	-	1[a]	-	-	-	1
meningitis	-	1	-	-	-	-	-	1
myoclonics/chills	-	-	-	1	-	-	-	1
henoch schonlein/kawasaki	1	-	-	-	-	-	1	2
kinsbourne	-	-	-	-	-	1	-	1
ITP	-	-	-	-	-	2	1	3
gait disturbance/ataxia/chorea	-	-	-	-	-	3	-	3
gastro-enteritis	1	-	-	-	-	-	-	1
diabetes mellitus	-	-	1	-	-	1	-	2
metabolic disease	-	1	1	-	-	-	-	2
pervasive/bevavioural disorder	-	-	-	1	-	6	-	7
intoxication	-	-	-	-	-	1	-	1
measles/whooping cough	1	-	-	-	-	1	-	2
infection/lymphadenitis colli	-	-	-	2	-	1	-	3
shaken baby-sy/intracranial haematoma	3	-	-	-	-	-	-	3
rumour	-	-	-	-	1	1	-	2
total	18	11	14	24	1	34	4	106

[a] dptp only
[b] once mmr0 before the first birthday

In one preterm born child there was a recurrence of apnoea while still on coffeine medication. It was concluded that this indirectly could be caused by the (stress of the) vaccinations. The one child with possible flaccid paralysis was vaccinated outside the Netherlands with Infanrix-hexa and hospitalised; we failed as yet to get the necessary information for assessment.

ITP was reported three times, twice following MMR1 with possible causal relation despite the fact that in one case essential information is still missing. In the case following DTP5 the interval was considered too long for causal relation. Twice the notification came in because of planned revaccination and once the event concerned a recent vaccination. One of the two children with metabolic/hereditary disorder had acute derangement with coma/encephalopathy and acute liver failure a day and a half after the second vaccination with DPTP/Hib, administered in hospital because of suspected metabolic disorder in an older sibling. (This older sibling died after the third vaccination. We have reported on this child in our 1999 report.) This child received a further Hib vaccination, in 2001, at the age of 13 months without problems and a fourth vaccination with Hib at the age of 15 months, also administered during hospital supervision, was also uneventful. A week later he developed an

upper airway infection at home and had a fatal derangement of a not yet defined metabolic disorder. In the report on 2001 this case will be commented upon further. The other child had Werdnig-Hoffman syndrome diagnosed some time after his third DPTP/Hib vaccinations; this disease bears no relation to vaccination. There was a clear increase in reports on behavioural problems compared to previous years following the adverse publicity about autism after MMR vaccination. All cases have been assessed very carefully but in none establishment of causal relation with the vaccination seems warranted. Of the four children with arthritis/discitis it was judged to be coincidental or not classifiable (1). In all other cases causality was judged to be improbable because of time interval and/or other established causes.

Table 16. Major illness and causal relation of reported AEFI in 2000

diagnosis⇓ causality⇒	certain	probable	possible	improbable	unclassifiable	total
high fever	-	14	29	3	-	46
crying/irritability	-	3	-	-	-	3
pallor	-	1	-	-	-	1
arthritis/discitis	-	-	-	3	1	4
apnoea/respiratory insufficiency	-	-	1	-	-	1
guillain barre/flaccid paralysis	-	-	-	-	1	1
pneumonia/ bronchiolitis	-	-	-	4	-	4
rash illness	-	-	-	7	-	7
vaccinitis	-	-	4	-	-	4
deafness	-	-	-	1	-	1
meningitis	-	-	-	1	-	1
myoclonics/chills	-	-	1	-	-	1
henoch schonlein/kawasaki	-	-	-	2	-	2
kinsbourne	-	-	-	1	-	1
ITP	-	-	2	1	-	3
gait disturbance/ataxia/chorea	-	-	2	1	-	3
gastro-enteritis	-	-	1	-	-	1
diabetes mellitus	-	-	-	2	-	2
metabolic disease (derangement)	-	-	1	1	-	2
pervasive/bevavioural disorder	-	-	-	7	-	7
intoxication	-	-	-	1	-	1
measles/whooping cough	-	-	-	2	-	2
infection/lymphadenitis colli	-	-	-	3	-	3
shaken baby-sy/intracranial haematoma	-	-	-	3	-	3
rumour	-	-	-	-	2	2
total	-	18	41	43	3	106

6.9.3 Persistent Screaming

In 2000, 39 children with persistent screaming were reported (in 1994-1999 respectively 37, 22, 16, 26, 29 and 34). Two children with possible persistent screaming are not included but only listed under discoloured legs as fierce crying seems to be part of the discoloured legs syndrome. Two children, one with discoloured legs and one with collapse reaction, are also included in the persistent screaming category because of the distinct presentation of the uncontrollable crying. The reported persistent screaming seems age/dose dependent, as has been noticed in former years (see table 6). Local symptoms were pronounced in nine cases, of which two mainly had (presumed) pain at the injection site and/or avoidance of movement of the legs. Some of the children had both sided local reactions. Additional symptoms were restlessness, feeding difficulty, and pallor. Parents were usually desperate and eight contacted

the family physician and five went to the hospital, with two admissions. We did not record the degree of intervention in four cases, however (table 9). In all cases the event was considered to be causally related (table 11).

6.9.4 General skin manifestations/phenomenon

In 2000 skin symptoms were the main or only feature in 75 reports (58, 74, 75 and 85 in 1996, 1997, 1998 and 1999). Discoloured legs are not included but are categorised separately. The numbers and the distribution over the different vaccine doses is rather similar to prior years, reported events most frequently following the first two DPTP/Hib vaccinations and the first MMR. See table 17.

Table 17. Skin symptoms and vaccines of reported AEFI in 2000

vaccine⇒ / symptoms⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dhx	mmr1	dtp5	dtp6/mmr2	other	total
angio-oedema/swelling	-	3	-	-		2	-	-	-	5
exanthema	5	13	3	1	1	10[a]	2[b]	2	1	38
cyanosis/flush	1	1	-	-	-	-	-	-	-	2
cutis marmorata	1	-	-	-	-	-	-	-	-	1
urticaria	3	3	-	3	-	1	-	3[c]	-	13
eczema (increase)	3[d]	4	1	1	-	1	-	-	-	10
petechiae	3	1	-	-	-	-	-	-	-	4
diaper rash	-	-	-	1	-	-	-	-	-	1
ringworm	-	-	-	-	-	-	-	1	-	1
Total	16	25	4	6	1	14	2	6	1	75

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

All events were considered minor. Exanthema, urticaria and (increased) eczema were the most frequent symptoms. Five times there was noted vasomotor swelling/angio-oedema and three times vasodilation/vasoconstriction with erythema/cyanosis or cutis marmorata. There were four children with petechial rash on upper body and/or face. Children with petechiae on the legs only are categorised under discoloured legs.

Table 18. Skin symptoms and causal relation of reported AEFI in 2000

causality⇒ / symptom⇓	certain	probable	possible	improbable	unclassifiable	total
angio-oedema/swelling	-	-	1	4	-	5
exanthema	-	2	16	18	2	38
cyanosis/flush	-	1	1	-	-	2
cutis marmorata	-	1	-	-	-	1
urticaria	-	-	4	8	1	13
eczema (increase)	-	-	5	5	-	10
petechiae	-	2	1	1	-	4
diaper rash	-	-	-	1	-	1
ringworm	-	-	-	1	-	1
total	-	6	28	38	3	75

14 Cases concerned MMR1 (once before the age of 12 months) with six times (possible)

causal relation. In only one of the six times MMR was combined with DTP there was a possible causal relation in which the symptoms could be caused by either vaccine. This resulted in possible causal relation with MMR in 35% with rashes in the second week after the vaccination (without systemic symptoms) or on the day of vaccination when causal relation could not be ruled out. The other events were not considered causally related with the vaccination, because of inconceivable time interval or other cause. For the other vaccines or combinations, possible causal relation was assessed in 28 out of 56 events (53%), with in the remaining events other causes assessed and/or non-plausible time interval.

6.9.5 Discoloured legs

Starting from 1995, discoloured legs are in a separate category, subdivided in blue, red or purple legs with diffuse or patchy discoloration, with or without petechial rash. Leg petechiae without noted discoloration are also grouped in this category.
In 2000 126 reports were received, comparable with 1998 and 1999 but higher than the three years before that (table19). Of these 23 were blue legs (18 double-sided), 46 red legs (31 double-sided) and 47 purple legs (42 double-sided). Of the 25 one-sided discoloration nine concerned the DPTP leg and six probably the Hib leg but in ten cases this could not be decided. In total, 31 children had petechiae, including 9 reports without noted prior discoloration of the legs (21 times both sided).
About 25% of the children had also fever of which one ≥40.5°C (also booked under major illness). Over 70% of the children exhibited fierce crying of whom four for three or more hours (two of these also categorised as persistent screaming). Injection site reactions, if any were not pronounced, but 17 times severe pain (once extreme) was noted/presumed, several times without other signs of inflammation. Seven children had also collapse reaction. These compound reports are grouped under collapse also. Eight children were reported with recurrent discoloured legs after subsequent vaccinations. Reports of discoloured legs were most frequent after the first DPTP/Hib vaccinations and decreasing in number with dose number and age, a familiar pattern over the years. Causal relation with the vaccines was inferred in all but three cases and twice the event was not classifiable because of lacking essential information. See table 11.

Table 19. Discoloured legs and vaccines of reported AEFI in 2000

vaccine⇒ / symptoms⇓	dptp/hib1	dptp/hib2	dtpt/hib3	dptp/hib4	dptp/hib?	dtp5	(petechiae)	total 2000	1999	1998	1997	1996	1995
blue legs	9	6	7	1	-	-	(5)	23	17	25	23	18	21
red legs	22[a]	16	4	2	1[b]	1	(10)	46	55	56	38	41	47
purple legs	22	11	12	2	-	-	(7)	47	30	30	23	27	19
petechiae only	5	1	2	2	-	-	(9)	9	28	14	11	13	6
total	58	34	25	7	1	1	31	126	130	125	95	99	93

[a] once hib only
[b] once discolouration unspecified

Further details of this specific adverse event will be published in a separate RIVM report (descriptive epidemiology and follow up of discoloured leg syndrome following childhood vaccinations, in preparation).

6.9.6 Faints

In this event category collapse (hypotonic-hyporesponsive episode, HHE), syncope (fainting) and breath holding spells (BHS) are listed (table 20). In 2000 there were 221 collapse cases, equal to 1999 (120, 145 and 158 in 1996, 1997 and 1998), five times BHS and 13 fainting in older children. The five children with breath-holding-spells turned blue, after stopping to breathe in expiration when fierce crying, with a very short phase of diminished responsiveness and no limpness or pallor.
The distribution of collapse over the different scheduled vaccines is, as we described before, in the majority of cases after the first DPTP/Hib vaccinations and numbers diminishing with dose number and age [28]. Numbers are similar to 1999, the year when the accelerated schedule was introduced but the old schedule still applied for part of the children. See for further information under introduction, chapter 1, and discussion, chapter 7.

Table 20. Faints and vaccines of reported AEFI in 2000

vaccine⇒ event⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dtp5	dtp6/mmr2	total 2000	1999	1998	1997	1996	1995
collapse	151[a]	41[b]	21	8[c]	-	-	221	221	158	145	120	137
bhs	4	-	1	-	-	-	5	5	4	4	7	2
fainting	-	-	-	-	6	7[d]	13	18	12	6	7	8
total	155	41	22	8	6	7	239	244	174	155	134	147

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

In 2000 there were five children with recurrent collapse reported, including the child that received DTP in stead of DPTP because of the prior collapse reaction. Some of these children had (very) incomplete episodes. In four children the collapse was considered not related because of the too long time interval and/or other cause. Once the event was non-classifiable. See also tables 10 and 11 for sex distribution and causality.

6.9.7 Fits

In this category (febrile) convulsions and epileptic seizures find a place. Also “atypical attacks” in case a definite diagnosis could not be made and convulsion could not be excluded either, are listed here. (See also paragraph 5.5)
Most reported convulsions were febrile, occurring predominantly after the fourth DPTP/Hib and MMR1 vaccinations. The reported non-febrile convulsions are very few and evenly distributed over the different doses; the atypical attacks tended to be most frequent in the first half year of life (table 21). Fits at the younger ages were less frequently accompanied by fever than at the later doses/older ages, more so in case of convulsions than in the atypical attacks. Altogether 12 children had fever of 40.5°C and over, twice in children with atypical

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

Table 21. Fits and vaccines of reported AEFI in 2000

vaccine⇒ / event ⇓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	mmr1	dtp5	total 2000	1999	1998	1997	1996	1995
febrile convulsion simple	-	-	-	14[a]	15	-	29	42	39	27	24	23
complex	-	-	2	11[b]	13	-	26	24	17	18	8	18
tonic	-	-	-	-	1	-	1	1	2	1	3	10
atypical	-	-	-	2	-	1	3	4	3	6	3	7
non febrile convulsion	-	1[c]	1	1	1	-	4	6	4	5	4	6
epilepsy	2[d]	-	2	-	3	-	7	3	3	5	3	3
atypical attack	17[e]	5	6	9	5	-	42	43	65	45	28	30
total	19	6	11	37	38	1	112	123	133	108	73	97

[a] once dptp only and once dptp/hib and mmr
[b] once dptp and mmr
[c] once temperature not mentioned
[d] once dptp only
[e] once dtp/hib

59 of the convulsions were febrile of which 48 possibly due to the fever caused by the vaccination and considered an adverse reaction. Of the febrile convulsions not considered to be causally related there was other cause established and/or an implausible time interval with the vaccination (seven following MMR1 and two after DPTP/Hib4 and one after DTP5). One report could not be classified because of missing information. Of the four non-febrile convulsions two were considered not causally related to the vaccination, one after MMR1 and one after DPTP/Hib3 administration. See also table 11.
There were seven children with epilepsy reported, three with (possible) West syndrome and one report with undefined epilepsy following a vaccination in 1966. All were considered not caused by the vaccinations with one of the epilepsies preceding the MMR vaccination.
42 Reports were classified as atypical attacks, in 31 cases possible causal relation to the vaccination. In this subcategory there were five children with possible chills and seven with myoclonics. Eight children turned blue and cyanotic, once with possible breath holding spell, four children were hypertonic and another seven limp. None of the children fulfilled the case definitions for collapse or convulsion.
In 1999 MMR was involved in 41 reports, in all but three instances as single vaccine.
23 Times causality was inferred with MMR and in three cases the event was attributed to the other simultaneous vaccines. Thus there was imputed causal relation with MMR in 58% (86% in 1999 and 69% and 66% in 1998 and 1997) and for the other vaccines in 78% (85% in 1999 and 87% and 76% in 1998 and 1997) of reported cases.

6.9.8 Encephalopathy/encephalitis

In 2000 there was one report of encephalopathy following DTP5. It concerned a boy of 4 years and 4 months who was mildly retarded because of stationary encephalopathy with suspected Aarskog syndrome. He had a slight cold but was otherwise healthy. He developed fever within half an hour after the vaccination. Late on the second day he developed

convulsions that were unresponsive to therapy unlike his prior febrile convulsions. He developed acute encephalopathy. Mycoplasma infection was detected. He had full recovery. It was concluded that this event was not causally related to the vaccination.

6.9.9 Anaphylactic shock

No cases were reported in 2000. In matter of fact, we have never received notification of anaphylactic shock with inferred causality and/or appropriate time interval in the few cases suspected anaphylactic shock was notified, since the surveillance system was installed.

6.9.10 Death

In 2000 three children were reported who died after a vaccination of the RVP (table 22). These were two boys and one girl. See case histories below. In only one case autopsy was performed. It should be stressed however that without full post mortal investigation a definite diagnosis is not possible. And in child B and C the autopsy is greatly missed. In all three children the symptoms following the vaccinations were only minor and only in child B there could have been some contribution of the (stress of the) vaccination. Without definite diagnosis however definite causality assessment is not possible either. All information considered however, including available scientific evidence it is considered unlikely that vaccination and death are causally related.

Table 22. Death and vaccines of reported AEFI in 2000

child	sex	age	vaccines	time interval		symptoms/diagnosis	causality*	autopsy
				illness	death			
A	female	2 months	dptp/hib1	minor	20 hours	intracranial hemorrhage in child with severe anaemia and syndrome of Townes-Brookes?	no	yes
B	male	2 months	dptp/hib1	minor	4 hours	severe cardiac malformation, Ivemark syndrome, cardiac arrest, shunt occlusion?	no?	no
C	male	5 months	dptp/hib3	minor	11 hours	clinical sids ?	no	yes

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

Child A, a girl of 2 months old received the first DPTP/Hib vaccinations. She had multiple congenital malformations and was suspected of Townes-Brooks syndrome and unexplained recurrent anaemia. After the vaccination she was somewhat tearful and had some local reaction with a possible haematoma. At night she drank her bottle and cried only when diaper changed. In the morning she refused to drink her first bottle and some hours later her breathing became suddenly shallow and she became unresponsive. It took some time before the father was reached. On the way to hospital she stopped breathing several times. When in hospital there were no brainstem reflexes more with insufficient breathing and slow heart rate. Resuscitation was unsuccessful. Autopsy revealed no cause of death, apart from the known malformations. The only abnormality was the sanguineous spinal tab and quite a lot of free blood intracranially.

Child B was a boy of two months who received his first DPTP/Hib vaccination. He suffered from Ivemark syndrome with severe cardial malformation for which he was operated 11 days

old (Blalock-Taussig shunt). He was on digitalis and diuretics medication and continuous antibiotics. After his vaccinations he cried for a short time. At home there were no problems with feeding nor his medication. Four hours after the vaccination he woke and was a little tearful but could be consoled with his pacifier and slept a little. When he woke up after ten minutes he cried again and refused his feeding. His temperature was 38°C. During the phone call with the GP he became suddenly gasped and turned pale blue. Within ten minutes, when the GP arrived he was panting breathing pattern with central and periferial cyanosis and tachycardia. Before the ambulance could be called he developed apnoea and had a heart rate of 20-30. Resuscitation was unsuccessful. Permission for autopsy was not obtained.
It is possible that the stress of pain and fever, not very pronounced at all however, have contributed to the (time of) death of this child, leading to possible cardiac failure. A more likely occurrence seems to be shunt occlusion, because that is a known complication in these cardiac malformations. The role of the vaccination in this remains only speculative and if any only indirectly.
Child C was a boy of five months old who died 11 hours after his third DPTP/Hib vaccination. Like the two prior vaccinations there was nothing in particular: he drank a little less and had possibly a slight temperature. An hour after he was put to bed he was found dead in supine position. Autopsy was not performed. The boy was born after 33 weeks gestation, after Caesarean Section with low Apgar Score, ventilation and phototherapy. He had a full recovery and growth and development were satisfactory. At the age of two months he was operated on congenital cataract.

7. Discussion

The safety of the RVP is guarded by an enhanced passive surveillance system. The exact number of vaccinations is known, because the PEA register all administered vaccines on an individual level[29,32] . The RVP is embedded in the regular Child Health Care with near total coverage, therefore the programme is delivered by a relatively small group of specifically trained professionals. This is also advantageous for safety surveillance. The operation of a (24h) central telephone information service for professionals is a most important tool in obtaining notifications and an efficient method both for the reporters and on the receiving end. The placement of this safety surveillance system at RIVM with its expertise should guarantee high quality.
But the Achilles' heel of passive surveillance is underreporting. Especially selective underreporting creates distortion. Therefore the representativeness of data on AEFI presented here, will be discussed.
The year under report was given special attention, since this is the first year in which the effect of the change in schedule from 3, 4, 5 to 2, 3, 4 months of age could be studied. The data of 2000 will be compared with those of 1998 for this purpose and commented upon[30] .
The success of the vaccination programme, having brought the target diseases under control, increases the relative importance of side effects. This increases the demands on the safety surveillance system. We will discuss the characteristics of the current system and comment on its strength and shortcomings. Mere registration of possible adverse reactions is not enough to sustain confidence in the safety of the programme. We will discuss how the information in the current system may play a role in the management of adverse events and in the risk-benefit communication to professionals and parents.
We will discuss the safety of the vaccination programme in the light of the here presented results of the passive surveillance system and consider future approaches.

7.1 Underreporting

Reducing underreporting is of special importance in passive surveillance systems, especially selective underreporting. Since 1994 we have put extra effort into this, as has been discussed in previous annual reports[22,23,24]. It has been concluded that the rise in number of reports in 1994-1997 resulted mainly from this effort, with a minor influence of the introduction of a new vaccine (Hib) from July 1993 onwards. The increase in number of reports in 1998 was held to be partly due to a further decrease in underreporting but also to some increase of real adverse reactions caused by the use of the higher potency pertussis component in the DPTP vaccine. Increased awareness may have played a role too[25] . The reports of 1999 were difficult to interpret since the change in schedule did not apply to the full calendar year but only to the children born in 1999 (and after) which resulted in vaccination of an extra number of children[45].
Some underreporting will have to be accepted. Both adverse events that are regarded clearly as adverse reactions and events that are considered evidently coincidental have a higher risk of not being reported. Also, with (almost) all (former) contraindications revoked, even some

severe adverse events may no longer be reported since the exact diagnosis is of no importance to subsequent vaccination and the need for consultation may not arise. It is of importance to secure reporting of these events because otherwise trend analysis and comparisons between different vaccines, schedules and lots, may be hampered. For picking up signals of unexpected or unsuspected late adverse reactions, passive surveillance systems are not a proper tool. Other designs need to be tried.
The level of underreporting seems satisfactorily low but one has to be vigilant all the same, and some specific events may need more attention.
See for discussion the sub paragraphs below.

7.1.1 Number of Reports

Since the step up of 1998 the reporting rate has stabilised. Compared to 1998 the small increase in reported adverse events is totally in line with the larger birth cohort, assuming a same vaccination coverage. (Coverage data are available only up till the cohort of 1998 as yet). The coverage has been very stable over the past years however. The (small) decrease compared to 1999 was to be expected since in 1999 an extra month cohort received the first three DPTP/Hib vaccinations, due to the new accelerated schedule. The capacity of the telephone service, the main route for reporting, has been very much under stress in 2000 and 2001, due to lack of manpower because of reallocation and job vacancies, with consequent inaccessibility. This may lead to "evaporation" of notifications, as has been known to happen before when the telephone service was flooded with calls in the period of the last polio epidemic when there was additional shortage of personnel because of illness and vacancies. We have received no signals that notifications have gone up in thin air in the year under report however, but complaints have been received. Reporters know of course that notification can also be done by mail. There is no increase in reporting by mail, however. The telephone service is also used for consultation and advice and since quite a high number of reports reach us because of the need for consultation, we have to assure that the telephone service is “open”, in order not to miss a substantial part of notifications.
The small increase of multiple reports seems of no significance and may be due to increased follow up efforts of the initial notification, by both RIVM and the original reporters. Also there have been more duplicate notifications of the same event by different sources. Those are counted as one report. It may be a sign of more complete reporting.
Reporting criteria have not changed over the years, but awareness of professionals and the public has increased lately, partly because of the publicity around new/to be introduced vaccines. Recently the need for vaccinations and their safety has been questioned by certain groups[36]. Public awareness of the seriousness of the target diseases has diminished since the illnesses have been effectively prevented for many years now[37]. Consequently more value is attached to potential side effects. This influences the readiness to report perceived adverse reactions. Reporting criteria for adverse events following immunisation are flexible and subject to personal interpretation and circumstances. Our system registers any notification, regardless the reporting criteria, time interval or causality.

7.1.2 Reporters

The vast majority of notifications are from Child Health Clinic staff. Nearly all children attend the Child Health Clinics, where professional standards require asking after adverse events at the next clinic visit. Therefore it is expected that few severe events are missed. In training courses we do however address reporting by paediatricians and child neurologists, especially of (severe) events or diseases after vaccinations which they themselves hold to be clearly coincidental but parents may (later on) regard as vaccine associated. It is important that hospital information is made readily available when clinic staff reported the event. Only then is it possible to counteract public unrest (pro-actively). This should also guarantee the ability of the surveillance system to detect new and hitherto unknown adverse events. Reporting by paediatricians or GP's may lead to earlier notifications. It does not make contact of the surveillance system with the Child Health Clinics unnecessary however, as the latter have valuable information on growth, development and health and of course data on the vaccines. Therefore we have asked clinic personnel to notify anyway, regardless of (supposed) reporting by others. This includes cases where they asked parents to report themselves or heard they did. Distribution over the different reporting sources has remained stable over the years however, except for an absolute and relative increase in reporting by parents.

Events that are more easily missed are those following vaccinations without a close follow up clinic visit. This will possibly affect MMR vaccinations to some extent and especially the revaccination at four and nine years of age. This may need extra attention in training and refresher courses. Also in the information leaflets for the parents it should be stated more explicitly that in case of severe or peculiar adverse events, parents should not only contact the GP but also the clinic. Active follow up as planned within the EUsafevac project should throw some light on the extent of underreporting of some adverse events following MMR1. See also paragraphs 7.4.4 and 7.6

7.1.3 Regional Distribution and Reporting Rates

We have standardised the number of reports per region on rate per 1000 vaccinated infants (for the first three doses). Since the actual numbers of vaccination coverage and population in the different regions are only available up till 1998 the rates for 2000 are based on these data. Apart from the slightly larger birth cohort (+3.6% according to CBS data) this is held to have little distorting influence. Regional reporting rates were not significantly different from the national average. Again this seems to point again to good reporting behaviour of the clinics and does not indicate regional underreporting. Perhaps it testifies a further decrease in underreporting.

7.1.4 Distribution over Vaccines and Dose

The distribution (relative frequency) of reported AEFI over the different (doses of) vaccines is rather similar to 1994-1999 (table 5 and figure 2). This gives no indication of selective underreporting and points to very stable reporting habits.

The increase in number of reports (3.8%) as compared to 1998, is in line with the increase in cohort size (3.6%), with for the first DPTP/Hib dose an increase of 12.4% and for all four

DPTP/Hib doses combined 3.0%. Numbers for the fourth dose of DPTP/Hib in 2000 are a little lower than in 1999, but higher than in 1998. This could well have been the result of a change in reporting attitudes with more (spontaneous) follow up of reported children. Some of the increase in the number of multiple reports may well reflect this phenomenon (40 cases in 2000, 44 in 1999 versus 26 in 1998 and 12/14 in 1996/1997). There seems also to be a tendency to postpone reporting of non-severe and non-contraindicating events until subsequent vaccinations have been administered and information about adverse events, if any, is collected. In cases the diagnosis is minor general illness, minor skin or local reactions the notification is regarded as just one report and listed according to the most pronounced/severe event or linked to the latest vaccination (see methods under paragraph 4.2). The accelerated schedule may have resulted in a more close watch on the first vaccination with increased reporting as a result. Since some of the here-discussed possibilities have opposite effect on reporting rates per dose it is hard to conclude anything just on the numbers. See also the paragraphs regarding the effect of the accelerated schedule (paragraph 7.2).

7.1.5 Distribution over Events

The distribution of reports across event categories is rather similar over the years (table 6 and figure 3). Also within each event category over the different (doses of) vaccines. Some increase/decrease may be random fluctuations. There is no indication of systematic underreporting. The reporting rate of collapse reactions and febrile convulsions is close to incidence rates shown by prospective studies[46,47,48] . Hower, background rates of most events are not known, and there may be (substantial) underreporting for some. For instance, the ITP reporting rate is lower than some studies suggest[49,50]. This needs to be studied through active surveillance design. Since reporting criteria include severe events regardless of assumed causal relation, perhaps all severe events, occurring in the applicable risk window for the specific event and vaccine, should be reported. The number of reported discoloured legs is rather stable over the early years, with perhaps a step up since the use of higher potency pertussis vaccine. However, we have no indication of the completeness of reporting of this specific event. Persistent screaming shows underreporting, in view of estimates in prospective studies (that did not apply uniform case definitions). However, during our assessment of the notifications of persistent screaming, verification showed that some reports did not fulfil the current case definition.

But it could also be that the change of schedule directly or indirectly influenced type and severity of reported events within event categories. There is no indication of a reporting bias. The increase in number of reported collapse reactions is most pronounced and warrants further investigation. See under paragraph 7.2

The percentage of assessed adverse reactions (with causality assessed as certain, probable or possible) is 79% and similar to 1998 (80%). The share of major events, by our definition, together with minor events with hospital admission increased from 56% and 54% in 1997 and 1998 to 58% in 2000. This may be fully due to the increase in reported collapse reaction since

the new schedule. Criteria for major events including hospitalisation do not reflect severity *per se* and are subject to numerous vaccine-unrelated factors.

7.2 Accelerated Schedule/Change in Schedule

The change in schedule since the 1999 birth cohort did not affect the reporting rate. The distribution over the different vaccine doses and events was rather similar to before. The younger age for the first three doses did not result in a shift in numbers and reported events. Therefore, reported events appear to be more dose- than age-specific. It is known that vaccination at a younger age has less fever and local reactions than at a later age has[51]. Since the event categories of minor and major general illness are very heterogeneous, the numbers presented here do not yield firm conclusions. However, the increase in major general illness is mainly due to MMR and the third and fourth dose of DPTP/Hib.
These vaccinations are not (much) affected by the new schedule. Moreover, the percentage of adverse reactions with assessed causality was a little lower than in 1998. There was a decrease in reported high fever after the first two DPTP/Hib doses. Active follow up, as planned for the EUsafevac project may include a subgroup to monitor vaccine tolerability at younger age. The main working diagnoses in the minor general illness category are fever and crying. Both were reported less in 2000 than in 1998. Pallor and/or cyanosis went up considerably. This increase may reflect the younger age when the vasomotor system is less stable. See also under collapse and discoloured legs below.

7.2.1 Collapse reaction

Reports of collapse reactions appear to have truly increased. Numbers and distribution over the vaccine doses have been rather stable over the past years, with around 100 reports of collapse following the first DPTP/Hib dose (at three months of age) and approximately 25 and 15 reports after the second and third dose. Since the change in schedule the total number of reported collapse reactions has gone up with 50% for the first dose at two months of age. (OR 1.55 c.i. 1.36-1.76) Extrapolation of the 1999 results over a full year also shows this increase. Distribution over different doses remained the same, however, which suggests a strong dose effect and a less pronounced age effect, since some increase of collapse occurred after the second dose. Otherwise the number of reported collapse reactions at three months of age would have been about 100 instead of the actually reported 40. We have reason to believe that this is not due to reporting bias or underreporting. Apparently, to some extent a previously received dose of DPTP/Hib vaccine protects against collapse reaction at three months of age. Cytokines/mediators/interleukins that are part of the primary immune response but are not formed (as much) following subsequent contacts with the antigens may play a role. We will comment on this in our report on collapse reactions (in preparation).
Five children with recurrent collapse after the first and second dose were reported, one of whom unsubstantiated and two with incomplete episodes. In only one case the pertussis component was skipped and the vaccination schedule continued with DTP/Hib; however, collapse reaction reoccurred. There are no indications that the accelerated schedule raises the risk of recurrent collapse substantially. Yet we will look into this more systematically next year.

7.2.2 Discoloured legs

Numbers of discoloured legs are similar to those in 1998. The above remarks on collapse reactions also apply here. Distribution over the different doses remained the same, without apparent effect of the younger age, suggesting a stronger dose than age effect. Otherwise the number of reported discoloured legs at three months of age would have to be about 50% higher that the actual reported number. Lacking incidence rates of discoloured legs from prospective studies, we can only speculate. The reporting rate of the discoloured leg syndrome has been constant since we made it a specific subcategory and applied case definitions. This does not suggest selective underreporting. We will try to estimate incidence rates in the active follow up within the EUsafevac project. We will report on discoloured legs in a separate publication (in preparation), in which some follow-up data will be included.
The number of compound reports with collapse reaction and discoloured legs is stable over the years (6, 6, 7, 8 and 7 in 1996, 1997, 1998,1999 and 2000). Whether the accelerated schedule increases the risk of recurrence of the discoloured legs or not remains to be seen. Recurrence does happen, not necessarily following the next dose, but remains without sequelae.

7.2.3 Apnoea

In 1999 and 2000 we had several reports of apnoeaic incidents in (extremely) premature children. This is apart from the apnoea in possible BHS or as part of convulsions. In most cases the episode was during primary hospitalisation with monitor surveillance. Some children were still on stimulants like coffeine and had prior and later apnoeaic episodes. With at least one child the episode occurred when it cried and appeared to have been possible BHS-like. Another child was diagnosed with septicaemia and most probably its cyanotic episode with respiratory insufficiency resulted from this.
No doubt there is substantial underreporting of this phenomenon. On the other hand, we may have been notified of apnoeaic episodes that would have occurred anyway without attribution to vaccination.
None of the episodes were medically riskful/severe, apart from one that was concluded to be part of sepsis/bacteriaemia and that was (most probably)not attributable to (the stress of) the vaccination.
Risk benefit balance of the vaccination in extremely premature children favours vaccination at an early age. Pertussis is extremely hazardous to them. Therefore the normal accelerated schedule may be applied for premature children

7.2.4 Severity, Reporting Interval and Causality of Reported Events

We have checked for the different severity markers/parameters, such as major versus minor events and level of intervention. Also the reporting intervals for different doses and events have been compared.
The increase in severity (major events and minor events with hospitalisation) is fully attributable to the increase in collapse reactions for the first two DPTP/Hib doses, while other categories show a slight *de*crease in severe events. For the third dose the increase in severe

events is not due to collapse reactions but to some increase in reported discoloured legs and atypical attacks.
The reporting interval, an indicator of severity or anxiety, shortened slightly, with 37.5% within 4 weeks (before the next clinic visit), compared to 33.4% in 1998. Increase in early reports was greatest with the first two doses of DPTP/Hib, viz. 8% and 10%, and 6% with the third dose. The reporting interval of MMR also decreased, with reporting within 4 weeks in 41% of all cases, a 7% increase over 1998 (it was 40% in 1999). This may have been caused by adverse publicity about safety of the MMR vaccine. Increased attention may have played a role, too, since MMR was distributed by another manufacturer in a different form and presentation in 1999 and 2000 (because of a temporary shortage of the regular product).
Only 33 reports had a very long time interval, of over two years to the vaccination date. This is a particular subset. In two thirds a causal relation was considered to be absent; in some the reported event occurred prior to vaccination. This subset of late reports had significantly more parents as reporters (18) and more frequent homeopathic intervention (7). Some perceived late effects of the vaccination had been fuelled in part by adverse media publicity about certain adverse events. In other cases the need for/or wisdom of revaccination was questioned in the light of a prior adverse event. Some of these cases may have been reported earlier and therefore not “missed” by the system. As electronic data are only available from 1996 onwards this can not be checked easily. At least three of these late reports were duplicate reports, one concerning diabetes, another epilepsy and a third ITP as far as we know now. (All have been included in this annual summary, because this was not known at the time the tables were made).
As for the first dose of DPTP/Hib, the percentage considered to be adverse reactions was the same in 1998 and 2000 (viz. 90%). For the fourth dose DPTP/Hib the percentage of adverse reactions was 85% both in 2000 and 1998. For MMR it was 50% in either year. The second and third dose had fewer reports in 2000 than in 1998 and the percentage attributable to vaccination decreased also (by 10%). There is no ready explanation for this in the change in schedule.
The increase in severity of the reported events under the accelerated schedule appears to be due to an increase in collapse reactions, with a higher number of hospitalisations and inherent anxiety/apprehension.

7.3 Specific Events

In addition to what is said in paragraph 7.1 and 7.2 on specific adverse events with regard to underreporting and effect of the accelerated schedule, some events or event categories are discussed below.

7.3.1 Convulsions and Atypical Attacks

The number of (classic) febrile convulsions following DPTP/Hib vaccinations was similar to 1998. This is not surprising since these events are most frequent after the fourth dose, and this dose is not affected by the change in schedule. No febrile convulsions after the third dose of DPTP were reported. This may reflect the younger age of this dose. The number of reports with atypical attacks was lower than in 1998 and comparable to 1997. One has to bear in

mind that this is a subcategory for non-specific paroxysmal events that do not fulfil the criteria for collapse or convulsion. So the number is (very much) subject to completeness of information. Thus, in different years transfer to and from other event categories varied. If planning and priorities permit, we plan to look into the phenomenon of atypical attack in more detail. The stable and low number of reports of non-febrile convulsions may reflect non-causality in the first place.

7.3.2 Local Reactions and Abscess

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

7.3.3 Skin Symptoms and Allergy

The number of reported skin symptoms remained remarkably stable over the years, with a similar distribution over vaccines and type of efflorescence. None of the reported cases were considered to be allergic reaction to the vaccines. With the change in schedule, we expect that more often than before signs of eczema in prone children will follow vaccination. This is not because the vaccine causes eczema but because of the natural history of atopic disease and the accelerated schedule since 1999. The numbers do not show increased reporting, however.

7.3.4 ITP, Gait disturbance (ataxia)

ITP numbers have remained low throughout the years. The rate of ITP after MMR1 in the literature is much higher than we get reported. The causal relation of ITP following other RVP vaccines remains speculative. An active surveillance study has been started from 2002 through NSCK in order to get more insight on ITP and its relation to vaccinations. Biologically, it is plausible that MMR may cause ataxia, but there is no systematic data. We get very few reports, maybe because of the lack of causal relation with the vaccine. This event is also included in the active surveillance study through NSCK.

7.3.5 Anaphylactic shock

Most feared of all is anaphylactic shock. We never had a report of anaphylactic shock caused by the current vaccines of RVP. After so many doses, apparently it does not occur with these vaccines. The practice advocated by IGZ of vaccinating all children in Child Health Clinic settings or mass vaccination at school age seems wise and the non-availability of emergency sets seems justified.

7.3.6 Encephalopathy

Encephalopathy following pertussis vaccination seems to be one of the “wrecks of once known and acknowledged truths strewn on the pathway of medicine” (citation of Barbara Tuchman). Since 1987 we have had no report of encephalopathy possibly attributable to DPTP (pertussis) vaccination. All events had other etiology, like chromosomal or genetic disorders, like Reye syndrome, virus or mycoplasma encephalitis, metabolic diseases or intoxication (salicylate or tramal eg). Also some vascular accidents like thrombosis with underlying clotting disorders have come to light. Lately some children with shaken baby

syndrome were reported. The increased possibilities to detect metabolic diseases and chromosomal or genetic disorders have greatly contributed to diagnostics in these kind of events, and so have virological tests, PCR and last but not least MRI.
Reports of encephalitis following MMR are rare. In a few instances causal relation could not be ruled out, since no definite cause could be identified and the event occurred in the risk window for MMR (1: 500,000-1,000,000 children). In the year under report, the only report of encephalitis followed DTP5 and was caused by mycoplasma infection.

7.3.7 Pervasive Disorders and Retardation

Press allegations about possible causal relation between MMR vaccination and autism dented the confidence of parents in the vaccination programme. Despite the fact that based on scientific evidence renowned (groups of) scientists have refuted these alleged associations, especially in the United Kingdom the vaccination coverage dropped considerably[52]. We have received some reports on behavioural problems in the autistic spectrum, often quite some years after the MMR vaccination. Some parents have no real suspicion but have been made insecure, others simply clutch the last straw.
In none of the reported cases a causal relation was found, and in some the event preceded the vaccination.
It is to be expected that reports of events that have attracted attention in the press will increase. A passive surveillance system, even an enhanced one, is not the proper tool for a refutation of false hypotheses. When/if appropriate and possible, systematic studies will be done in close international collaboration.

7.3.8 Epilepsy

In the past years a number of studies have been done on the etiology of epilepsies[53]. Current scientific opinion holds that vaccines do not cause epilepsy. However, it may not be possible to exclude this definitely in an individual case. Vaccines may cause convulsions, mainly indirectly through fever. As for West syndrome, epidemiological evidence refutes a causal relation[54]. However, the age at which it occurs coincides with the vaccination schedule.

7.3.9 Death

This year three children were reported. In view of the average over the years, this is in line with expectations. Systematic studies and evaluation of the Institute of Medicine have shown infant death to be unrelated to childhood vaccinations[55]. In an individual case, this may not be demonstrated easily. Especially in the case of possible SIDS this poses a problem. Diagnosis of SIDS is possible only after extensive post-mortem examination has not revealed a cause of death. Therefore it is of utmost importance to insist on full post-mortem investigations and to report fully on all infant deaths following vaccinations. Even if causation is very remote, it is known that in the direct surroundings of the case there is an adverse effect on compliance to the programme, of public and professionals.
In the year under report, once the vaccination might have had an (indirect) adverse role in the death of the infant. This child had a severe malformation of the heart as part of a syndrome. Since no autopsy was performed, the cause of death could not be determined. Because of the

time frame, indirect involvement of the vaccinations could not be ruled out. Because the child did not have fever and did not cry excessively, the vaccination may not have caused very much stress. Possibly there was shunt occlusion, a frequent complication, and the role of the vaccination remains speculative. It could be discussed whether compromised children like this child should be vaccinated. Not vaccinating these children, will relieve the vaccine or vaccination programme of the burden of suspicion, but it might be argued that this is not in the interest of the child. Especially children with underlying heart-, lung- or neurological disease have more to fear from infection than other children have. So the risk benefit balance favours vaccination. Pain or fever prophylactics may be indicated. Sometimes one may opt for vaccination in hospital day-care.
In the other two children causal relation was judged to be unlikely, even if a definite cause of death could not be established.

7.4 Safety Surveillance of the RVP

Safety surveillance of the vaccination programme seems to be of increasing importance[7,8,43,56]. The surveillance system will need to be supplemented by more active monitoring and systematic studies. Passive surveillance will remain the backbone however. For purposes of follow up and other forms of systematic study homogeneous event categories with application of case definitions are the core.
Assessing causal relation is essential in monitoring the safety of the vaccination programme[39,41,40,42,56]. Of course, after vaccination does not mean caused by vaccination. Only 1.6% percent of the reports did not allow a causality assessment, mostly because of lack of information about time interval or symptoms. All unclassifiable events were considered non-severe or were unsubstantiated rumour, except for one of the children who died (in this case causality was judged to be unlikely however). Overall 79% of reports were considered adverse reaction compared to 80% in 1998. Comparison of RIVM with GR assessment shows remarkable consistency. Safety surveillance with causality assessment by RIVM and GR makes it possible to use wide reporting criteria, which leads to more sensitive signal detecting. Since adverse events without presumed causal relation are covered by the system, signal detection is included irrespective of time period covered. Five different categories are used for causal relation for the purpose of international comparison. However, international comparison is hampered by different criteria for surveillance systems, diagnostic procedures, causality assessment and inconsistent case definitions. On top of that, different schedules and/or vaccines are used.

7.4.1 Route of Reporting and Feedback

We hold that the telephone service is an important tool in the safety surveillance of the RVP, both for capture of important adverse events or potential adverse reactions and with regard to the quality of data. This low threshold reporting channel has great advantage over written report forms not only because of superior possibility of communication, timeliness and supplementation of data. It is also an important tool for adherence to the programme and to promote proper use of contraindications and adequate vaccination in special circumstances.

It makes very efficient use of resources, which may be less obvious at the level of RIVM than in the broader perspective of management of the vaccination programme as a whole.
Education of potential reporters, while essential, will not yield much gain in efficiency for the type of reports received in a passive surveillance system. One has to bear in mind that adverse events reported in passive surveillance systems are in majority severe and/or rare events and uncommon peculiar or unexpected events or, in case of more common events, concern special circumstances or specific underlying problems. One cannot expect that health care professionals know what specific information is needed for any specific event, age and vaccine and keep up with all medical literature in this respect. Education which stresses the importance of reporting and explains the type of basic information necessary to keep at hand when reporting, may contribute to further efficiency gains.
There seems to be an increasing need for the public also to have access to this kind of information service. More readily available and accessible printed general and specific information is needed, both for professionals and the public.

7.4.2 Verification and Assessment

In the monitoring of the safety of the vaccination programme, verification and additional information with follow up is considered of utmost importance. A substantial part of supplementation and verification is done in the reporting telephone call. With written notifications this will have to wait until later.
Categorisation is according to diagnostic criteria for case definitions and for causality. For the aggregated analysis all cases have been reappraised. Discrepancy is often large between reported diagnosis and final diagnosis. This discrepancy is partly due to different case definitions, but also because of more detailed information and more specific knowledge, skills and experience of the physicians of RIVM. The value of a detailed account by the parents, especially in case of paroxysmal events, can not be overrated. Careful history taking after the first panic has subsided is of great importance[27,42]. 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 with other severe events more frequently seen. One tends to mould symptoms in known diagnostic categories. But on the other hand, reported collapse reaction is not always collapse. Often there is only pallor or only apathy or just drowsiness or excessive sleep/difficulty in awakening and symptoms do not meet the criteria for the case definition.
Skin symptoms tend to cause great concern because of feared anaphylactic reactions following a next dose. Like in former years most children with skin symptoms, even if apparent/occurring in close time relationship with the vaccination, get a subsequent dose without recurrence. Severe anaphylactic reactions have not been known to happen with the vaccines of the RVP. We prefer descriptive terms for skin symptoms as well as for other categories, with no reference to possible pathophysiological mechanisms, like allergic reaction for which there seems no justification most of the time.

The use of strict case definitions assures homogeneous diagnostic groups with possibility of epidemiological studies for risk factors and sequelae. Together with follow up this may lead to founded adjustment of indications, contraindications, vaccines or schedules as well as to proper precautions when administering a next dose. For collapse reactions this kind of follow up study has shown a very low rate of recurrence after further pertussis vaccinations[27,42].

7.4.3 Source of Information and Intervention

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

7.4.4 Passive Surveillance versus Active surveillance

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

7.5 Management of Adverse Events

The increasing relative importance of potential side effects makes careful surveillance of the safety of the vaccination programme even more important. Just signal detection isn’t enough anymore. (See also under paragraph 7.4) Evaluation and feedback communication should complement mere registration. Information about reported adverse events should have a place

within the risk communication to parents. Some side effects are unavoidable but where possible the aim should be to prevent side effects. Adverse coincidental events are unavoidable however. Sometimes postponement of vaccination might free the vaccine and vaccination programme of allegations of causing an event or disorder that will inevitably occur. But deferral or postponement should be avoided as much as possible because it will delay protection of the child.

7.5.1 Prevention and Treatment of Side Effects

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

7.5.2 Contraindications

Contraindications for the RVP vaccines have been abandoned more or less completely[27,28,30,39,40]. Proper application of true contraindications should be adhered to however to prevent undue side effects. But false contraindications should be avoided because they lead to missed opportunities to provide protection. In the year under report abandoned contraindications do not seem to have contributed much to the number of reported events. And therefore prevention of side effects will not gain much in using more strict contraindications and only result in a loss of protection.

7.5.3 Risk Communication

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

7.5.4 Causality Assessment

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

7.6 Considerations for the Safety Surveillance of the RVP

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

Active surveillance to check on overall tolerability may be realised as part of an EU project (EUsafevac). Furthermore the tolerability of the currently used vaccines might be measured, partly in the phase II and III trials in which the registered vaccines are used in the control groups. However hypothesis testing cannot ever be done within the same system as the system the that generated the hypothesis.

The newly introduced acellular pertussis vaccine as a booster dose in the four year old (from birth cohort 1998 onwards) will be followed up actively and this study may serve as a pilot for the EUsafevac project. Hospital admission after any vaccine, gait disturbances and ITP after MMR1 are the proposed events to be studied in (prospected) active design. These studies may shed light on ITP and gait disturbances as adverse events and on the relative performance of the current passive surveillance system.

A well performing, good quality safety monitoring system such as exists in the Netherlands should not be taken for granted but requires maintenance and investment. New epidemiological designs and techniques may expand our knowledge of adverse events and an adequate database system is a prerequisite for this. The data put into the system must be of good quality. After successful prevention of the target diseases the relative weight of adverse events increases. Parents and providers expect careful safety monitoring of the vaccinations. Anti-vaccine-movements will be more active in the future. A comprehensive surveillance system will be instrumental in refuting unfounded allegations.

Providers must be supplied with timely referenced information about any suggested association of severe adverse events and vaccination in the media or medical press. This will enable them to answer questions from the public. Clinic staff stress that convincing parents of the benefits of the vaccination programme takes more time than before than before and that resources lack. Often parents already have information from other sources and it is not easy,

if at all possible, for them to decide on its quality. The sites of anti-vaccine movements on the Internet are much more readily accessible than the more balanced information about the merits of the programme. Also there is need for fact sheets per target disease and vaccine. Periodic actualisation of the RVP guideline book is also necessary but will not meet the need for timely information to refute unfounded allegations. Lately the Minister of Health has recognised this need in a letter about the RVP to the parliament (2nd of October 2000).

8. Conclusions and Recommendations

In 2000 the number of reports stabilised since the introduction of the higher potency pertussis component in the DPTP vaccine in 1998. Overall the acceleration in schedule since the 1999 birth cohort has not lead to an increase in reports. The increase in reported collapse reactions and the shift of collapse and discoloured legs howeve may shed light on the pathophysiology of these phenomena. This will be subject to further study.
Periodically the overall tolerability of vaccines used in the vaccination programme should be studied with attention to perceptions of providers and parents. The change in schedule from birth cohort 1999 onwards to an earlier start of the programme makes direct comparison with prior studies not entirely possible anymore, however. The EUsafevac project study may supply some information on the tolerability of the vaccine, as may the planned field trials of new vaccines (combinations).
Overall regional distribution of reports seems very satisfactory, although there seems to be substantial underreporting of some adverse events. We have included ITP and gait disturbances (ataxia) following (MMR) vaccination in one of our data linkage pilots. (EUsafevac). Detailed study of epidemiology, sequelae, follow up and risk factors should be performed about some specific adverse events, e.g. collapse, discoloured legs and atypical attacks/non-febrile convulsions in the near future. Also we will look into the abscess cases for risk factors.
The telephone service for reporting, consultation and advice is an efficient and important tool of the enhanced passive safety surveillance system and in the management of the RVP. Quality should be maintained and if possible its performance studied.
The planned database system for adverse event surveillance should allow further detailed aggregated analysis of the reports and also facilitate systematic feed back to the reporters as well as data exchange with other bodies, nationally and internationally.
Safety surveillance systems 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 that introduction in the RVP of more (novel) vaccines is foreseen in the forthcoming years. This information will be necessary to counteract allegations of anti-vaccine movements. A problem is that one can not know what the next signal will be. International collaboration should be expanded, in order to move towards a comprehensive safety surveillance network of childhood vaccination programmes. This may also help perform needed specific studies and increase scientific knowledge about adverse events following vaccinations. Eventually this will boost public confidence in the programmes.
For the coming year are planned:

- implementation of a robust database system
- accelerated annual report on 2001
- maintenance and evaluation of the current passive surveillance system
- report on descriptive epidemiology of discoloured legs and follow up with regard to the accelerated schedule

- belated report on descriptive epidemiology of collapse reactions and follow up, including the effect of the accelerated schedule
- exploration and study of possibilities of data linkage or sentinel studies, with start of some events in the NSCK prospective monitoring
- design of active study of tolerability of DPTP/Hib vaccinations, also in relation to the accelerated schedule with start of the programme at a younger age.
- active follow up of the new acellular pertussis booster vaccine of the four year old children

We plan to keep up a thorough high quality safety-surveillance-system and to stimulate reporting in the coming year. Thus, one can show that the vaccination programme is safe. The total of 1142 reports must be seen in relation to a total of nearly 2.5 million vaccines administered with over 6 million components.

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Appendix 1 Mailing list

1	Hoofdinspecteur Preventieve en Curatieve Gezondheidszorg
2	Directeur-Generaal Volksgezondheid
3	Inspectie Gezondheidszorg, Inspecteur Infectieziekten, J van Wijngaarden
4	Inspectie Gezondheidszorg, Insecteur JGZ en RVP, A. Ambler-Huiskens
5	Gezondheidsraad, Den Haag, voorzitter
6	Gezondheidsraad, Den Haag, secretaris werkgroep bijwerkingen RVP
7	Gezondheidsraad, Den Haag, secretaris werkgroep uitbreiding RVP
8-22	Safety Surveillance Systems (diverse buitenlandse instellingen)
23	Depot Nederlandse Publikaties en Nederlandse Bibliografie
24	Directie RIVM
25	Directeur sector Vaccins/NVI
26	Directeur sector Volksgezondheidsonderzoek
27-29	Hoofd LER/LTR
30	LER/LTR
31	LVO
32	Hoofd LCB
33	Hoofd LPO
34	Hoofd LVR
35	Hoofd KRZ
36	Hoofd CIE
37	CIE
38	Hoofd LIO
39	Hoofd LIS
40	Dr J Schellekens
41	Directie SVM
42	Apotheker SVM
43	College ter Beoordeling van Geneesmiddelen
44	Lareb
45	J.Labadie
46	Dr H.C. Rumke, Vaxinostics, EUR, Rotterdam
47	LVE
47-65	Medisch Adviseurs Entadministraties
66	Landelijke Vereninging Entadministraties
67	LCI
68	LCR
69-75	Auteurs
76	SBC/Communicatie
77	Bureau Rapportenregistratie
78	Bibliotheek RIVM
79-89	Bureau Rapportenbeheer
100-140	Reserve

Appendix 2 Vaccination Programme 2000

Voor de Hib-entingen geldt dat in het kader van het Rijksvaccinatieprogramma alleen kinderen geboren vanaf 1 april 1993 voor vaccinatie in aanmerking komen.

5.6 De Gemeentelijke Geneeskundige en Gezondheidsdiensten van Amsterdam en Rotterdam zijn wat betreft de administratieve verzorging van het Rijksvaccinatieprogramma gelijkgesteld met de Provinciale Entadministratie.

5.7 Alle nadere regelingen welke met betrekking tot het Rijksvaccinatieprogramma 2000 worden getroffen, vereisen de goedkeuring van de Algemeen Hoofdinspecteur voor de Gezondheidszorg.

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

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

6 BIJWERKINGEN

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

7 VACCINATIESCHEMA PER KIND

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

Den Haag, december 1999

De Wnd. Algemeen Hoofdinspecteur voor de Gezondheidszorg

drs. *P.H. Vree*

STAATSTOEZICHT OP DE VOLKSGEZONDHEID

Inspectie voor de Gezondheidszorg

RIJKSVACCINATIEPROGRAMMA 2000

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

2000	1999	1996	1991
DKTP + Hib	DKTP + Hib + BMR	DTP	DTP + BMR

1. ZUIGELINGEN en KLEUTERS

Vaccinatieschema

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

  Op de leeftijd van respectievelijk **2**, **3** en **4** maanden wordt één DKTP-injectie gegeven.
  Er dient minimaal een periode van 4 weken in acht te worden genomen tussen de drie opeen volgende vaccinaties. De vierde DKTP-injectie wordt bij voorkeur gegeven op de leeftijd van 11 maanden. Er dient tenminste een tussenperiode van 6 maanden in acht te worden genomen tussen de derde DKTP-injectie en de vierde DKTP-injectie.
  Dosering: 1 ml INTRAMUSCULAIR.

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

  Indien de kinkhoestvaccinatie gecontraïndiceerd is (zie R.J.F. Burgmeijer en D.J.A. Bolscher "Vaccinaties bij kinderen", 3e herziene druk, Van Gorcum 1998) en in plaats van DKTP, DTP wordt gegeven, dient 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 **2**, **3** en **4** maanden wordt één Hib-injectie gegeven.

  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.

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Er dient minimaal een tussenperiode van 4 weken in acht te worden genomen tussen de drie opeenvolgende vaccinaties. De vierde Hib-injectie wordt bij voorkeur op de leeftijd van 11 maanden gegeven. Er dient tenminste een tussenperiode van 6 maanden in acht te worden genomen tusen de derde Hib-injectie en de vierde Hib-injectie.
Dosering: 0,5 ml INTRAMUSCULAIR.

- **BMR** (Bof - Mazelen - Rodehond)

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

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

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

  De in 1996 geboren kinderen worden in 2000 gerevaccineerd met DTP-vaccin. Afhankelijk van de reeds vroeger gegeven entingen worden 1, 2 of 3 injecties gegeven (zie R.J.F. Burgmeijer en D.J.A. Bolscher "Vaccinaties bij kinderen", 3e herziene druk, Van Gorcum 1998).
  Dosering: 1 ml INTRAMUSCULAIR.

2 SCHOOLKINDEREN

Vaccinatieschema

De in 1991 geboren kinderen worden in 2000 gerevaccineerd met DTP-vaccin. Afhankelijk van de reeds vroeger gegeven entingen worden 1, 2 of 3 injecties gegeven.
Dosering: 1 ml INTRAMUSCULAIR.

De in 1991 geboren kinderen krijgen in 2000 een BMR-injectie.
Dosering: 0,5 ml SUBCUTAAN.

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

3 SIMULTANE VACCINATIES EN REGISTRATIE VAN PARTIJNUMMERS

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

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

4 ENTADMINISTRATIES

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

Provincie	Adres	Telefoon	Fax
GRONINGEN	Gorechtkade 8, 9713 CA Groningen	050-3686350	050-3122733
FRIESLAND	Gorechtkade 8, 9713 CA Groningen	050-3686350	050-3122733
DRENTHE	Lauwers 9, 9405 BL Assen	0592-395260	0592-352169
OVERIJSSEL	v. Reeuwijkstraat 50, 7731 EH Ommen	0529-455717	0529-455805
FLEVOLAND	v. Reeuwijkstraat 50, 7731 EH Ommen	0529-455717	0529-455805
GELDERLAND	Korte Coehoornstraat 2, 6811 LB Arnhem	026-4429242	026-4434999
UTRECHT	Zoutkamperschans 7, 3432 TZ Nieuwegein	030-6081376	030-6081517
NRD-HOLLAND	Zeilmakerstraat 40, 1991 JC Velserbroek	023-5382454	023-5386822
AMSTERDAM	Nieuwe Achtergracht 100, 1018 WT Amsterdam	020-5555460	020-5555360
ZD-HOLLAND	Europaweg 141, 2711 EP Zoetermeer	079-3418238	079-3315047
ROTTERDAM	Schiedamsedijk 95, 3011 EN Rotterdam	010-4339517	010-4339652
ZEELAND	Hollandiaplein 1, 4461 GT Goes	0113-249246	0113-249240
NRD-BRABANT	Bosscheweg 57, 5056 KA Berkel-Enschot	013-5400688	013-5400086
LIMBURG	Dalderhaag 13, 6136 KM Sittard	046-4529910	046-4584479

5 ALGEMEEN

5.1 Organisatie
De uitvoering van de vaccinaties wordt verzorgd door onder andere thuiszorgorganisaties en GGD's, onder verantwoordelijkheid en medisch toezicht van de entadministraties en in overeenstemming met de richtlijnen van de Algemeen Hoofdinspecteur voor de Gezondheidzorg.

5.2 Vaccindistributie
De vaccins worden door de SVM (Stichting tot bevordering van de Volksgezondheid en Milieuhygiëne) afgeleverd aan de Provinciale Entadministraties. De distributie 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 Rijksvaccinatieprogramma of in bijzondere omstandigheden volgens richtlijnen te geven door of namens de Minister van Volksgezondheid, Welzijn en Sport.

5.3 Registratie en verantwoording
De vaccinaties worden bij de Provinciale Entadministraties geregistreerd en verantwoord aan de hand van de terugontvangen oproepkaarten.

5.4 Financiering
De kosten van de uitvoering van het Rijksvaccinatieprogramma 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 Rijksvaccinatieprogramma. Voor vaccinaties in het kader van het Rijksvaccinatieprogramma door de thuiszorg of GGD behoeven de ouders geen bijdrage te betalen.

5.5 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 Rijksvaccinatieprogramma.
Dit geldt uitsluitend voor de DKTP-, DTP- en BMR-entingen.

Appendix 3 Package Insert DKTP

RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEU

040004

Difterie-, Kinkhoest-, Tetanus-, Poliomyelitisvaccin

Samenstelling
1 dosis (1 ml) bevat:

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

gemanoveerd poliovirus:

type 1	40	DE **
type 2	4	DE
type 3	25	DE
aluminiumfosfaat	1,5	mg
2-fenoxyethanol	5	mg
formaldehyde	25	µg

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

Farmaceutische vorm en presentatie
Difterie-, Kinkhoest-, Tetanus-, Poliomyelitisvaccin (DKTP) vaccin is een suspensie voor injectie en wordt afgeleverd in:
flesjes á 1 ml (1 dosis) bestelnr. 340.1

Fabrikant en registratiehouder
RIVM, Postbus 1, 3720 BA Bilthoven
afd. verkoop SVM
Postbus 457, 3720 AL Bilthoven
tel.: 030-2786019

RVG nummer
DKTP vaccin is in het register ingeschreven onder RVG-nummer 11640.

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

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

Speciale waarschuwingen en bijzondere voorzorgen bij gebruik
DKTP vaccin mag onder geen voorwaarde intravasculair worden toegediend.

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

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

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

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

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

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

Interacties met andere geneesmiddelen en andere vormen van interactie
DKTP vaccin kan gelijktijdig op verschillende injectieplaatsen worden toegediend met andere vaccins. Er zijn geen gegevens bekend over mogelijke interactie van DKTP- met BMR vaccin. Indien DKTP vaccin niet gelijktijdig met andere vaccins wordt gegeven, dient na een eerder gegeven gelijktijdig toegediend vaccin een interval van 1 weken en na een eerder gegeven levend vaccin een interval van 4 weken in acht genomen te worden.

Dosering en wijze van toediening
Een dosis DKTP vaccin is 1 ml en dient diep intramusculair te worden gegeven. Een volledige immunisatie bestaat uit een primaire serie van drie DKTP entingen en een eerste revaccinatie. De periode tussen de opeenvolgende vaccinaties is ten minste 2 maanden met een interval van tenminste één maand, en dient vóór de leeftijd van 6 maanden te zijn voltooid volgens een tijdige beschikbaarheid. De eerste revaccinatie (DKTP-4) wordt tenminste 6 maanden na de laatste entinig van de primaire serie gegeven. Met name ook premature geboren kinderen volgen dit schema volgens de Nederlandse leeftijd, zonder correctie voor de te vroege geboorte. Dit schema wordt in het Rijksvaccinatieprogramma toegepast.

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

Gebruik gedurende zwangerschap en het geven van borstvoeding
Geen bijzondere voorzorgen.

Bijwerkingen
Na toediening van DKTP vaccin kunnen lokale reacties optreden, de soms gepaard gaan met verschijnselen van algemene malaise en koorts. In zeldzame gevallen kan de kinkhoest component in het vaccin aanleiding geven tot een ernstige reactie zoals collaps of convulsie. Ook treedt sporadisch een toestand van encefalopathie na DKTP vaccinatie op, maar hierbij is een oorzakelijke relatie niet aannemelijk. Dergelijke complicaties worden waargenomen in een periode van 1 uur tot 3 dagen na enting. De meest ernstige reacties worden binnen 12 uur gezien. Alle ten wordt verzocht mogelijke bijwerkingen te melden aan Afd. Klinisch Onderzoek van het Laboratorium Veldonderzoek Vaccins van het RIVM, tel: 030 - 274 24 74

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

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

Appendix 4 Package Insert DTP

RIJKSINSTITUUT
VOOR VOLKSGEZONDHEID
EN MILIEU

0400113

Difterie-, Tetanus-, Poliomyelitisvaccin

Beschrijving en samenstelling
DTP vaccin is een gecombineerd vaccin tegen difterie, tetanus en poliomyelitis.
Difterie- en tetanustoxoïde: Aan bereid uit toxines geproduceerd door respectievelijk Corynebacterium diphtheriae, stam Parke Williams nr. 8 en Clostridium tetani, stam Harvard 49105. De poliomyelitiscomponent bestaat uit gekweekte en gezuiverde virus van de 3 typen: type 1 stam Mahoney, type 2 stam MEF 1 en type 3 stam Saukett.
Aan het gecombineerde vaccin zijn als conserveermiddelen 2-fenoxyethanol en formaldehyde toegevoegd.

1 dosis (1 ml) bevat:		
difterie-toxoïde	≥ 5	IE*
tetanustoxoïde	> 20	IE
gekweekveerd poliovirus:		
type 1	40	DE**
type 2	4	DE
type 3	7,5	DE
aluminiumfosfaat	1,5	mg
2-fenoxyethanol	5	mg
formaldehyde	0,025	mg

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

Farmaceutische vorm en presentatie
DTP vaccin is een suspensie voor injectie en wordt afgeleverd in:
flesje à 1 ml bestelnr. 340.1
flesje à 10 ml bestelnr. 340.10

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

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

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

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

Speciale waarschuwingen en voorzorgen bij gebruik
Na enige tijd staan, ontstaat een bodinktel. Dit is een normaal verschijnsel en is niet van invloed op de kwaliteit van het vaccin.
Alvorens het vaccin te gebruiken, moet het flesje enkele malen geschud worden tot een homogene suspensie is verkregen.
De kleur van het vaccin wordt vervolgens 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 fabrikant zegt niets over overschrijding van de bewaartemperatuur.

Dosering en wijze van gebruik
Een dosis DTP vaccin is 1 ml en dient intramuscular te worden gegeven.
Een basisimmunisatie voor reizigers wordt gegeven door een primaire serie van twee doses, met tenminste 1 maand tussengelegd 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 DKTP-vaccinatie langer dan 15 jaar geleden heeft plaatsgevonden dient de basisserie als ongeschikt beschouwd te worden.
Kinderen die een volledige basisimmunisatie met DKTP vaccin (4 doses) hebben ondergaan, 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 op twee 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 Voldenderzoek Vaccins van het RIVM, tel. 030-2742424.

Bewaring
Bewaren bij 2-8 °C, na bereiding is het vaccin onbruikbaar.
Multidoses flesjes zijn bedoeld voor groepsvaccinatie 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.

Dec-ember 1997

Appendix 5 Package Insert Hib

RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEU

040265

Haemophilus b conjugaat (PRP-T) vaccin

Haemophilus influenzae type b conjugaat vaccin gerriesdroogd

Gestandaardiseerd Gezuiverd Weinig bijwerkingen Lange houdbaarheid

Beschrijving en samenstelling
Haemophilus influenzae type b conjugaat (PRP-T) vaccin bestaat uit Hib (PRP-T) vaccin, is een gevriesdroogd vaccin waarbij het kapselpolysaccharide, polyribosylribitol fosfaat (PRP), gekoppeld is met difterietoxoïd als drager eiwit. Het vaccin wordt aangeleverd met de bijgeleverde reconstituerende oplossing.

Het gereconstitueerde vaccin bevat:
- polysaccharide-eiwitconjugaat met tetanustoxoïd (PRP-T) 10 µg polysaccharide
- tris (hydroxymethyl)-aminomethaan 0,6 mg
- sucrose 42,5 mg

Het vaccin bevat geen adjuvantia of conserveermiddelen.

Farmaceutische vorm en presentatie
Hib (PRP-T) vaccin is een poeder voor injectievloeistof en wordt afgeleverd in flesjes à 1 dosis en verpakt met eveneel flesjes reconstituerend vloeistof bestaande, 3M

Fabrikant
Pasteur Mérieux sérums et vaccins

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

RVG nummer
Hib (PRP-T) vaccin is in het register opgenomen onder RVG-nummer 17633.

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

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

Speciale waarschuwingen en voorzorgen bij gebruik
Zoals bij elke vaccinatie wordt, gedurende het toedienen van Hib (PRP-T) vaccin uit te stellen bij koorts of bij een acute infectie. Hib (PRP-T) vaccin mag niet intraveneus worden toegediend.
Alhoewel er tot op heden geen profylactische reactie bekend is van het vaccin worden vastgesteld, verdient het aanbeveling om een epinefrine-injectie en corticosteroïden beschikbaar te hebben en zonodig, geïnformeerd naar leeftijd en lichaamsgewicht, toe te dienen.
Hib (PRP-T) vaccin beschermt niet tegen infecties veroorzaakt door andere serotypes van Haemophilus influenzae dan serotype b, noch tegen meningitis veroorzaakt door andere micro-organismen.
In geen enkel geval kan het tetanus toxoïd van het vaccin de gewone anti-tetanus vaccinaire vervangen.

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

Dosering en de wijze van toediening
Gebruik voor reisprofylaxe uitsluitend de bijgeleverde reconstituerende vloeistof.
Resuspensie geschiedt door 0,6 ml van de reconstituerende vloeistof met een sterile spuit bij het gelmogde vaccin te voegen. Door het product voorzichtig om te roeren ontstaat een heldere, kleurloze oplossing. Een dosis bestaat uit 0,5 ml vaccin, ongeacht de leeftijd. Het vaccin dient binnen een uur intramuscülair te worden toegediend.

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

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

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

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

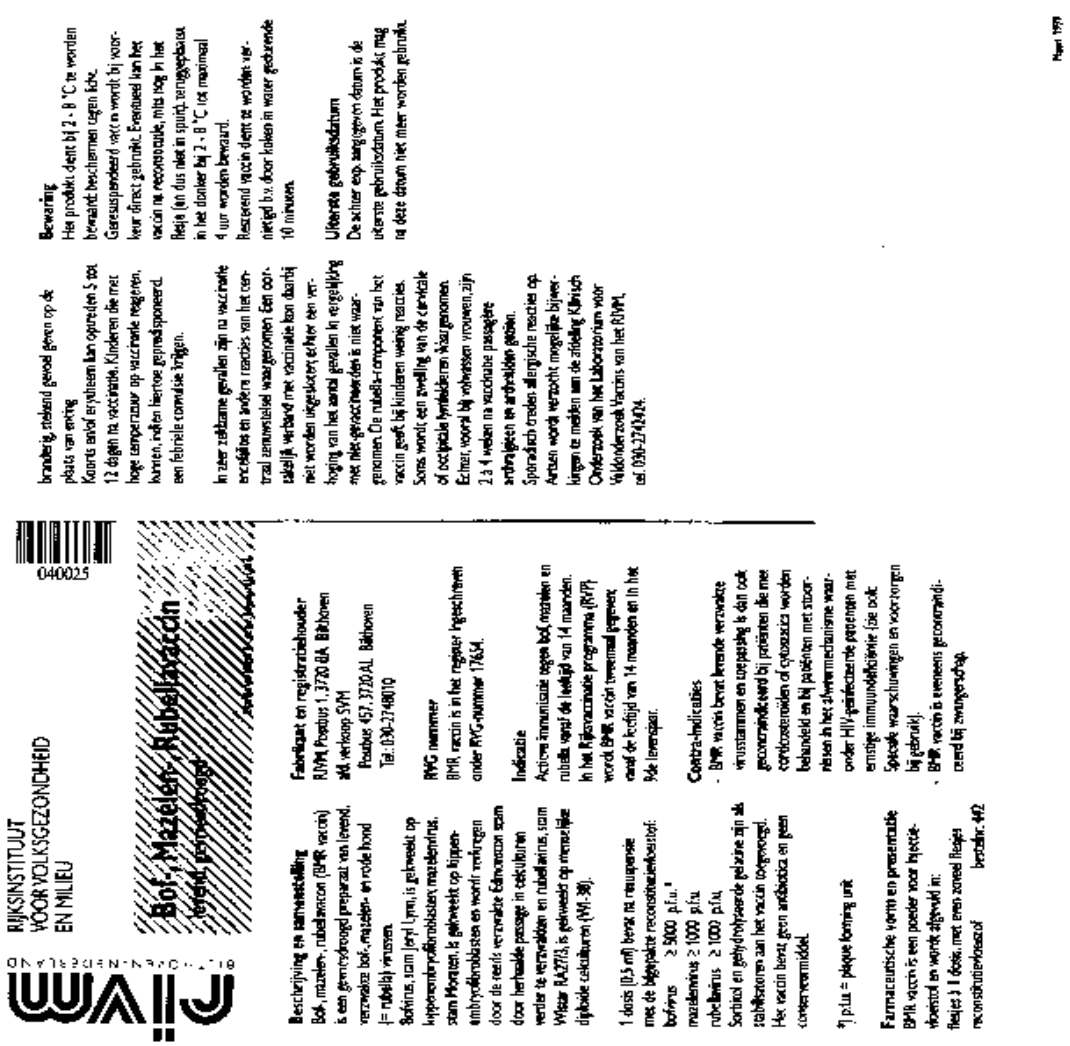
Bijwerkingen
Na injectie van Hib (PRP-T) vaccin kunnen lokale reacties voorkomen, zoals pijn, roodheid en zwelling. In een aantal gevallen treedt koorts op. Ernstige algemene reacties zijn niet bekend.
Artsen wordt verzocht ernstige bijwerkingen te melden aan de afdeling Klinisch Onderzoek van het Laboratorium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

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

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

Augustus 1999

Appendix 6 Package Insert BMR



Appendix 7 Package Insert MMR

DENOMINATION ET GROUPE

M-M-R® VAX

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

Groupe pharmacothérapeutique: vaccins contre la rougeole, les oreillons et la rubéole

NOTE À L'INTENTION DES MÉDECINS

INDIQUÉ DANS

Remarques particulières
Nourrissons

Vaccination des adolescentes et des femmes adultes qui ne sont pas enceintes, avec le vaccin contre la rubéole - pour le vaccin trivalent (M-M-R VAX) ou pour le vaccin monorubéolique seul.

Vaccination des femmes qui viennent d'accoucher, avec le vaccin contre la rubéole - pour le vaccin trivalent (M-M-R VAX) ou pour le vaccin monorubéolique seul.

COMMENT L'UTILISER ET EN QUELLE QUANTITÉ

Utilisation chez d'autres vaccins

CAS OU L'USAGE DU MÉDICAMENT DOIT ÊTRE ÉVITÉ

EFFETS NON DÉSIRÉS

DÉNOMINATION ET GROUPE

M-M-R® VAX

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

Groepsnaam

Voor gebruik in de geneeskunde

INDICATIES

Bijzondere opmerkingen

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

Inenting van pas bevallen vrouwen met het vaccin tegen rodehond - door middel van het gecombineerde vaccin (M-M-R VAX) of door middel van het vaccin tegen rodehond alleen.

Inenting van pas bevallen vrouwen met het vaccin tegen rodehond - door middel van het gecombineerde vaccin (M-M-R VAX) of door middel van het vaccin tegen rodehond alleen.

HOE GEBRUIKEN EN HOEVEEL

GEBRUIK SAMEN MET ANDERE VACCINS

OMSTANDIGHEDEN WAARBIJ HET GEBRUIK VAN HET GENEESMIDDEL MOET WORDEN VERMEDEN

ONGEWENSTE EFFECTEN

FABRIKANT

HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

BEZEICHNUNG UND GRUPPE

M-M-R® VAX

(LEBENDVAKZINE GEGEN MASERN, MUMPS UND RÖTELN, MSD)

Hinweis für Ärzte

Pasteur Mérieux MSD