

RIVM report 000001 002

**Adverse Events Following Immunisations
under the National Vaccination Programme
of The Netherlands**

Number II - Reports in 1995

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

Erratum

Figure 1 on page 27 has to be replaced with this one.

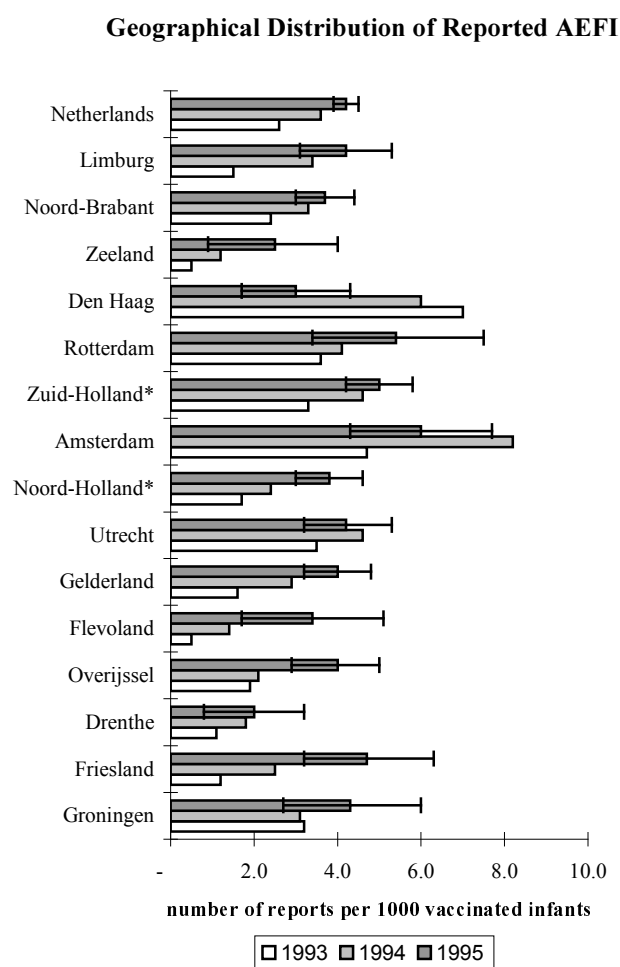


Figure 1. Number of reported AEFI in 1995 per 1000 vaccinated infants

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 1995 an overview of all received AEFI is presented with classification according to case definitions and causality. Reporting bias, background rates of specific events and possible pathophysiology of symptoms are discussed. On a total of approximately 2 million vaccinations 800 AEFI were submitted. Of these 1% (8) was unclassifiable because of missing information. In 81% (641) of the classifiable events a possible causal relation with vaccination was established and in 18% (151) the events were judged to be coincidental. Compared with 1994 there was again a rise in the number of notifications. Thorough evaluation revealed no increase of true side effects in the Netherlands but a further decrease in underreporting.

Acknowledgements

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

Abbreviations

AE	Adverse event (melding of postvaccinale gebeurtenis)
AEFI	Adverse Event Following Immunisation
AR	Adverse Reaction (bijwerking)
BCG	Bacille Calmette Guérin (vaccine)
CB	Child Health Clinic (consultatiebureau)
CIE	Centre for Infectious diseases Epidemiology (of RIVM)
DTP	Diphtheria, Tetanus, (inactivated) Polio (vaccine)
DPTP	Diphtheria, Tetanus, (whole cell) Pertussis, (inactivated) Polio (vaccine)
EPI	Expanded Programme on Immunisation
GGD	Municipal Public Health Department
GP	General Practitioner, Family physician (huisarts)
GR	Health Council (Gezondheidsraad)
HepB	Hepatitis B (vaccine)
HBIG	Hepatitis B Immunoglobulin
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
Hib	Haemophilus influenzae type b (vaccine)
IGZ	Inspectorate of Health Care
IPV	Inactivated Polio Vaccine
JGZ	Child Health Care (jeugdgezondheidszorg)
LVO	Laboratory for Clinical Vaccine Research (of RIVM)
MAE	Medical Consultant of PEA
MMR	Measles Mumps Rubella (vaccine)
PEA	Provincial Immunisation Administration
PMS	Post Marketing Surveillance
PRP-T	PolyRibositol 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. 96% van de spontane meldingen komen telefonisch binnen, in hoofdzaak vanuit de Jeugdgezondheidszorg. Nadere gegevens worden van ouders, huisarts of ziekenhuis verkregen in circa 50% van de meldingen. Na aanvulling en verificatie volgt het stellen van een (werk)diagnose en causaliteitbeoordeling door artsen van het RIVM. De beoordeling wordt meestal (70%) telefonisch teruggerapporteerd naar de melder. Schriftelijk verslag, veelal van de ernstiger of gecompliceerdere beelden, wordt naar alle medisch betrokkenen gestuurd. Een speciale commissie van de GR herbeoordeelt deze 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 ongeacht ernst of vermeend causaal verband in een kalenderjaar. Dit is het tweede jaarrapport.

In 1995 zijn 800 meldingen binnengekomen, betreffende 786 kinderen, op een totaal van meer dan 2 miljoen vaccinaties. Hiervan was 1% (8) niet te beoordelen wegens het ontbreken van informatie; in geen geval echter betrof het mogelijk ernstige bijwerking. 81% van de meldingen werd als bijwerking beoordeeld met een mogelijk, waarschijnlijk of zeker causaal verband. Een toevallige samenloop was er in 18% (151) van de meldingen.

Van de milde algemene of lokale verschijnselen (374) werden 272 (73%) meldingen als mogelijke bijwerking uitgeboekt.

Verkleurde benen (dit jaar voor het eerst afgesplitst van de huidverschijnselen) werden 93 keer gemeld, met op drie na een mogelijke causale relatie.

Ernstiger postvaccinale gebeurtenissen (gerubriceerd onder convulsies, collaps, persistent screaming en “ziek major”) werden 328 keer gemeld en in 85% beoordeeld als mogelijke bijwerking. Collaps, waaronder ook atypische en onvolledige episodes, werd 137 maal gediagnostiseerd, met slechts in drie gevallen geen oorzakelijk verband. Daarnaast twee keer Breath-Holding-Spells (2) en flauwvallen (8) in oudere kinderen. De 64 gediagnostiseerde convulsies, waarvan 58 febriel, werden op vier na alle gezien als mogelijke bijwerking. De 30 atypische aanvallen (57% met koorts) hadden in 60% een mogelijk causaal verband. Epilepsie (3) werd niet als bijwerking beoordeeld, maar als een coïncidentie. Alle meldingen van persistent screaming (22) werden gezien als bijwerking. Koorts van $\geq 40.5^{\circ}\text{C}$ trad op bij 35 kinderen uit de “ziek major” groep, in 54% als bijwerking beoordeeld, en nog eens 16 maal als onderdeel van een ander beeld, vooral van koortsstuipen. Van de 25 andere beelden uit de “ziek major” groep was er slechts twee keer een mogelijk causaal verband, bolle fontanel (1) en ITP (1). De overige 23 waren coïncidentieel. Er waren twee abscessen, beide met positieve kweek.

De meeste meldingen betroffen DKTP en Hib vaccinaties (660). BMR was betrokken in 114 gevallen, waarvan 25 maal gecombineerd met andere vaccins; in 54% was er een mogelijke causale relatie.

Voor de andere vaccin(combinatie)s was dit percentage 86%.

Vergeleken met 1994 was er een stijging in het aantal meldingen van ruim 12% ten gevolge van een verdere afname van onderrapportage.

Summary

Adverse Events Following Immunisations (AEFI) under the Netherlands Vaccination Programme (RVP) have been monitored by the National Institute of Public health and Environment (RIVM) since 1962. From 1984 onwards evaluation is done in close collaboration with the Health Council (GR). The 24h-telephone service for reporting and consultation is an important tool for this passive enhanced surveillance system. 96% of reports come in by telephone. Parents, GP's and/or hospital provide additional data on request (50% 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 (70%). 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 in detail 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 second annual report. In 1995, on a total of over 2 million vaccinations, 800 AEFI were submitted, concerning 786 children. Of these only 1% (8) were not classifiable because of missing information (all were minor events). 81% (641) of classifiable events were judged to be possibly, probably or definitely causally related with the vaccination and 18% (151) of the events were coincidental. Minor local or systemic symptoms were registered in 374 cases of which 272 (73%) were classified as possible adverse reactions. Discoloured legs, this year for the first time a separate category, were reported 93 times, with a causal relation more or less likely in 90 cases.

Major adverse events occurred in 328 cases (faints, fits, persistent screaming and general major illness) in 85% (279) a possible adverse reaction. All five death cases were considered chance occurrences. Collapse, including atypical and incomplete episodes, was diagnosed 137 times, in three cases with no causal relation. Twice breath holding spells and eight times fainting in older children were reported. Convulsions were diagnosed in 64 cases, 58 of which were febrile, all but four with inferred causality. Atypical attacks (57% with fever) were diagnosed 30 times, of which 60% with a possible causal relation. Epilepsy (3) was not considered causally related with the vaccinations. All 22 cases of persistent screaming were considered to be adverse reactions. Fever $\geq 40.5^{\circ}\text{C}$ was present in 35 cases of the major illness group, 54% of cases with inferred causality. Another 16 times high fever was part of another specific event, mainly febrile convulsions. Of the other 25 major illness cases only two had a possible causal relation, bulging fontanel (1) and ITP (1). The other 23 were considered to be unrelated. Major local reactions occurred in six cases, two of which were abscesses (culture positive, β haemolytic streptococcus A).

Most frequently reports involved DPTP and Hib vaccinations. MMR was involved 114 times, 25 times with simultaneous other vaccines; in 54% (61) of cases there was a possible causal relation. For the other vaccine combinations this percentage was 86%.

Compared to 1994 the number of reports rose, apparently reflecting a further decrease in underreporting.

1. Introduction

Identification, registration, and assessment of adverse events following drug-use are important aspects of post marketing research. Safety surveillance is even more important in the programmatic use of preventive strategies and intervention, especially when young children are involved. In the Netherlands the National Institute of Public Health and Environment (RIVM) has the task of monitoring adverse events following immunisations (AEFI) under the National Vaccination Programme (RVP). Already in 1962 with the introduction of the combined Diphtheria, Tetanus, whole-cell Pertussis and inactivated Polio vaccine (DPTP) a passive surveillance system has been adopted. Since 1984 the safety of the RVP is evaluated in close collaboration with the Health Council (GR). The annual reports of GR limit themselves to advising the Minister of Health on the safety issue of the RVP. These GR reports bear no reference to year of vaccination or adverse event nor to year of notification but only to year of reassessment by GR; therefore they do not permit comparing rates and nature of adverse events between different vaccines, schedules or vaccine lots. The introduction of a vaccine against *Haemophilus influenzae* type b (Hib) coincided with a change in the procedure of registration and assessment of AEFI by RIVM in 1993. The annual reports on adverse events by RIVM are based on the year of notification. They include all reported events, irrespective of severity of symptoms or causal relationship with the vaccination. Reported events are ordered by assessed nature and severity of the symptoms and causal relation. This 1995-report also contains a description of the procedures for soliciting notifications, verification of symptoms, diagnosis according to case definitions, and causality assessment. We will discuss some specific adverse events and their relation to the vaccination. Special attention will be given to underreporting and to prevention of adverse events and contra-indications. This RIVM report on adverse events is issued in English for the first time. Therefor it includes a more 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 a better knowledge and understanding of (adverse) effects of vaccines beyond the pre-registration research. This is particularly relevant for the identification of rare as well as late adverse reactions, as their rate of occurrence can only be estimated after vaccine use in large populations over a long time.¹ Insight in overdose consequences or use in special groups or circumstances or interactions can be gained only through PMS.¹ Moreover actual field effectiveness of many or most vaccines and vaccination programmes can only be determined after use over a long time in unselected populations. The surveillance of the RVP is a task of the National Institute of Public Health and Environment. The safety surveillance is done by the Laboratory for Clinical Vaccine Research (LVO) and the surveillance of the effectiveness by the Centre for Infectious Disease Epidemiology (CIE).² Requirements for post marketing surveillance of adverse reactions have been stipulated in Dutch and European guide-lines and legislation.^{3,4} The World Health Organisation (WHO) advises on monitoring of adverse events following immunisations against the target diseases of the Extended Programme on Immunisation (EPI) and on implementation of safety surveillance in the monitoring of immunisation programmes.⁵ The WHO keeps a register of adverse events as part of the global drug monitoring programme.⁶

Close evaluation of the safety of vaccines is of special importance for maintaining public confidence in the vaccination programmes 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 neurologic side effects caused a steep decline in vaccination coverage of pertussis vaccine and resulted in a subsequent rise of pertussis incidence with dozens of deaths and hundreds of children with severe and lasting sequelae of pertussis infection.

To counteract similar (unfounded) disquiet in The Netherlands RIVM has looked for a broader framework of safety surveillance, with a more scientific approach and independent reassessment. This led to the installation of a permanent committee of the Health Council (GR) in 1984. This committee reassesses the more serious events presented by RIVM. The GR advises the Minister of Health on the safety of the Vaccination Programme with annual reports. Since the GR reports have no direct reference to year of notification or vaccination and contain only a selection of reported adverse events they cannot be used for analysis of trends or patterns in reporting or events nor for comparison of vaccines, lots or schedules. The annual reports of RIVM on adverse events aim to contribute to these goals, however. We hope they will lead to better understanding of pathogenesis and risk factors of specific adverse reactions. In turn, this may lead to changes in the vaccine or vaccination procedures or schedules and adjustment of precautions and contra indications.

3. The National Vaccination Programme of The Netherlands

3.1 Vaccines and Schedule

In The Netherlands mass vaccinations of children were undertaken from 1952 onwards, with institution of the National Vaccination Programme in 1957. From the start all vaccinations covered were free of charge and have never been mandatory. Although a law existed on smallpox vaccinations this law has never been enforced. With the eradication of smallpox, this law was revoked in 1978 and smallpox vaccinations were abandoned.¹⁰ At first mono-vaccines against diphtheria, tetanus and pertussis were used and the combined DTP vaccine since 1957. After the polio epidemic of 1956, vaccination against poliomyelitis was added. There has been an intensive catch-up programme for all post World War II birth cohorts. From 1961 on the supply of nationally produced inactivated polio vaccine (IPV) was sufficient to meet the demands. From 1962 onwards the combined DPTP vaccine, with an enhanced polio component (1978), is in use for vaccination of infants and young children and DTP(olio) for revaccination of older children. Rubella vaccination for 11 year old girls was added in 1974 and measles vaccination for 14 months old children in 1976. In 1987 the combined measles, mumps and rubella (MMR) vaccine replaced the mono-vaccines in a two dose schedule for all children (14 months and 9 years). Mid 1993 vaccination against (invasive) infection with *Haemophilus influenzae* type b (Hib) was added for children born after April 1st 1993. In contrast to all earlier vaccines no catch up schedule was provided for, and a country-wide public information programme to advise parents on the benefit of vaccination of all children up to 5 years of age was not undertaken. The actual RVP of 1995 is included in Box 1 (Appendix 2)

Box 1. Schedule of the National Vaccination Programme of the Netherlands in 1995

3 months	DTP1 + Hib1
4 months	DTP2 + Hib2
5 months	DTP3 + Hib3
11 months	DTP4 + 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 2-6). BCG vaccination is not included in the RVP. Vaccination is offered only to those children with higher chance of acquiring tuberculosis when travelling to or staying in countries with a high prevalence. Usually vaccination takes place in the second half-year of life.¹⁰ Hepatitis B vaccination (HepB) is available for children of HBsAg positive mothers. These vaccinations are given, following HBIG administration at birth, in a four dose schedule at the ages of 3, 4, 5 and 11 months during the regular child health clinic visits. In Amsterdam, with a higher prevalence of HBV carriers, a different schedule and delivery system is operational. Children of refugees and those awaiting political asylum have an accelerated schedule.¹⁰

3.2 Vaccine Distribution and Registration

Vaccines for the RVP are supplied by SVM/RIVM and are kept in depot at a regional level at the Provincial Immunisation Administration (PEA). The PEA are responsible for further distribution to the providers. They also have the task to implement and monitor cold chain procedures at the child health clinics and municipal healthcare centres. The Medical Consultant of the PEA (MAE) guards and promotes programme adherence.^{10,11}

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. Returning of the cards is stimulated by reimbursement of the costs of vaccinating (approx. 5 Euro per vaccine). All administered vaccinations are entered in the databases of the PEA on an individual level; the PEA sends reminders to the child's address if necessary. The databases serve also the providers who can check the vaccination status of individual children, or of the population they serve. These data of the PEA follow the child when it moves from one place to another.

3.3 Child Health Care System

The Child Health Care system (JGZ) aims at enrolling all children living in the Netherlands.¹² 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. Up till 4 years of age (Pre School) children attend the Child Health Clinic (CB), regularly. At school entry the Municipal Health Care Service (GGD) takes over. From then on the Child Health Care gets a more population based approach, with special attention to risk groups and fewer individual check-ups. The first contact with the family usually occurs less than a week after birth when a nurse visits the home for the heel prick test on phenylketonuria and congenital hypothyroidism (PKU/CHT). At a special home visits approximately two weeks after birth, parents get information individually about Child Health and an invitation for the first CB visit at one month of age. Additional house calls may be made by the nurse.

In the first year of life about ten clinic visits take place during which physical check-ups are done. These include full medical history and growth and developmental screening at appropriate ages and tests of vision and hearing. Weight, height and head circumference are measured and recorded on growth charts. Validated test forms are used for developmental follow-up. Data on physical examination are also recorded in a standardised form. Advice on food and supplements is provided and information about behaviour, safety issues and upbringing is given. 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 alternatively by a nurse or a physician specially trained in Child Health. On individual basis this schedule may be adjusted, and house calls may be made by the nurse. The National Vaccination Programme is fully embedded in the Child Health Care system and vaccinations are given during the routine visits. Good professional standards include asking explicitly after adverse events following vaccination at the next visit and before administering the next dose. Booster vaccinations with DTP and MMR are usually organised in mass vaccination settings, with a possibility for catch up till the age of 13 years. (For refugees and asylum seekers up till 19 years). Attendance of Child Health Clinics is very high, up to 99% and vaccination coverage for DTP and Hib is over 97% with a slightly lower uptake for MMR of $\pm 95\%$.¹³

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's may also be reported by mail or fax.

The annually distributed vaccination programme (appendix 2) by the Inspectorate of Health Care (IGZ) encourages healthcare 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 B). Most municipal and regional child Health Care organisations, which provide the vast majority of vaccinations have explicit guidelines for notifying adverse events to LVO-RIVM. The

countrywide used guideline book on the RVP with background, execution and procedures, contains a (LVO-RIVM written) chapter on possible side-effects and gives ample information on notification procedures.¹⁰ LVO-RIVM promotes reporting through information, education and publications, for instance by contributing to refresher courses for child health clinic staff. Family physicians and paediatricians are informed at symposia and lately also during their training. Feedback to the reporter of AE's and other involved professionals has been an important instrument in keeping the reporting rate at high levels.

Severe symptoms irrespective of medical intervention and irrespective of assumed causality are to be reported. Furthermore peculiar, uncommon or unexpected events, and events that give rise to apprehension in parents, Health Care providers or may lead to adverse publicity. Events that lead to deferral or cessation of further vaccinations are considered as serious and therefore should be reported, too (see box 2).

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

- | |
|---|
| <ul style="list-style-type: none">- serious events- uncommon events- symptoms affecting subsequent vaccinations- symptoms leading to public anxiety or concern |
|---|

All notifications are accepted, registered and assessed by LVO-RIVM, irrespective of nature and severity of symptoms, diagnoses or time interval. No discrimination is made for official reports or consultations. After receipt of a notification, the information is reviewed by a physician of LVO-RIVM. Data are verified and the need for additional information is established. Additional information may be obtained from clinic staff, parents, gp 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 is assessed. The feedback includes a description of verified symptoms, the diagnosis and causality assessment of LVO-RIVM, and advice on subsequent vaccinations. See for more detailed description on procedures chapter 5.

Since 1984 The Health Council (GR) re-evaluates reported AE on the basis of formal detailed written assessment 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. Since 1994, for reasons specified in chapter 2, LVO-RIVM makes an annual report on adverse events and no longer indirectly via reports by GR. For further details see paragraph 5.7.

4. Materials

4.1 Post Vaccination Events

Events following immunisations do not necessarily have a causal relation with the vaccination and some have a temporal association only and are in fact mere coincidental.^{8,14} 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 without a presumed causal relation.
- **Side effects or adverse reaction:** an adverse event with a presumed or supposed or assessed causal relation with the vaccination.

Adverse events are thus divided in coincidental events and genuine side effects. Side effects are further subdivided in vaccine or vaccination intrinsic reactions, vaccine or vaccination potentiated events, and side effects through programmatic errors (see Box 3).¹⁵

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 a 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)

With very few exceptions notifications concern just one person. In case of *cluster* notifications special procedures are followed because of the potential of signal/hazard detection. If assessed as non-important, minor symptoms or unrelated minor events, cluster notifications are booked as one single report. In case of severe events the original cluster notification will, after follow-up, be booked as separate reports and are thus booked as several single, multiple or compound reports.

Box 4. Subdivision of notifications of adverse events

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

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

5. Methods

5.1 Analysis

The processing and evaluation of notifications of adverse events is directed by a standard operating procedure (SOP nr 12 N-GCP-08). Each notification is reviewed by a physician. 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 pathophysiologic mechanism of symptoms and alternative or other plausible causes of the event. The reporting physician 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 is 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, medical history, etceteras are usually obtained in the notifying telephone conversation with the 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 rarely parents may be visited by a physician from LVO-RIVM, at home or at the local Health 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 has exactly happened and when, and predisposing factors and underlying disease and circumstances have been established, causality will be assessed. This requires adequate knowledge of epidemiology, child Health Care, immunology, aetiology and differential diagnoses in paediatrics. The nature of the vaccine and its constituents determine which side effects it may have and after how much time. Causal relation will then be appraised on the basis of a checklist, resulting in an indication of the probability/chance that the vaccine is indeed the cause of the event. This list is not (to be) used as an algorithm although there are rules and limits for each point of consideration. (see box 5)

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

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

After establishing to what extent the vaccine or vaccination have attributed to the event, its causality will be classified under one of the five listed different categories. (box 6)

Certain (conclusive, convincing, definite), if the vaccine is proven to be the cause or if other causes are ruled out definitely; there should be a high specificity of the symptoms and a fitting interval.

Probable causal relation, if there are no signs of other causes, but a fitting interval and a satisfactory biologic plausibility of vaccine/vaccination as cause of the event. If, however, there are other possible causes or the time interval is only just outside of the acceptable limits or symptoms are rather unspecific the causal relation is classified as *possible*. If a certain, probable or possible causal relation is established the event is classified as adverse reaction or side effect. If a causal relation is regarded as (highly) *improbable*, there is only a temporal relation or a definite other cause for the symptoms; the event is then regarded as coincidental. This category includes also events without any causal relation with the vaccination. If data are insufficient for a (working) diagnosis and causality assessment, the event is listed under *unclassifiable*.

If a causal relation is regarded as (highly) *improbable*, there is only a temporal relation or a definite other cause for the symptoms; the event is then regarded as coincidental. This category includes also events without any causal relation with the vaccination. If data are insufficient for a (working) diagnosis and causality assessment, the event is listed under *unclassifiable*.

Box 6. *Criteria for causality categorisation*

1-Certain	involvement of vaccine vaccination is conclusive through laboratory proof or mono-specificity of the symptoms and a proper time interval
2-Probable	involvement of the vaccine is acceptable with high biologic plausibility and fitting interval without indication of other causes
3-Possible	involvement of the vaccine is conceivable, because of the interval and the biologic plausibility but other 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 causality assessment

By design of the RVP most vaccinations contain multiple antigens and single mono-vaccines are rarely administered. Therefore, even in case of assumed causality, attribution of the adverse events to a specific vaccine component or antigen may be difficult if not impossible. Sometimes with simultaneous administration of a dead and a live vaccine, attribution may be possible because of the different time intervals involved.

5.5 Event Categories

After assessment, all adverse events are classified under one of the ten different categories listed and clarified below. Some categories are subdivided in minor and major according to the severity of symptoms. A separate category, from this year on, are the discoloured legs, for the purpose of aggregated analysis. Formerly these events were either classified under skin symptoms or under local reactions (see also box 7).

- Local (inflammatory) symptoms: consist of inflammation symptoms and other signs around the injection sites which are classified as minor if they are not extensive and are of limited duration. Atypical or unusual mild or moderate symptoms at the injection site are included in this category. Inflammation which 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 which cannot be specifically categorised. For instance fever, respiratory or gastro-intestinal symptoms, crying, irritability, changed sleeping pattern or feeding behaviour, upper airway infection, 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 major category. Fever of 40.5°C and over is listed, by consent, as major general illness, except if associated with febrile convulsion. Prolonged mild or moderate fever is considered minor illness.
- Persistent screaming: (sudden) screaming, non-consolable and lasting for three hours or more, without one of the other specific diagnostic groups being applicable.
- General skin symptoms: skin symptoms which 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 circumscribed lesions distant from the injection site are included and the harlequin syndrome is booked under skin symptoms as well. Also some mild systemic symptoms may be present. Subdivision is made according to severity in minor and major if applicable.
- Discoloured legs: symptoms are diffuse or patchy discoloration of the legs and or petechiae, with or without swelling. Extensive local reactions are not included. Subdivision according to severity in minor and major may be made if appropriate.
- Collapse or Faints: a sudden loss of consciousness, loss of muscle tone and pallor, unless it is explicable as post-ictal state or part of another disease entity. If symptoms are incomplete or atypical this is added as an annotation. Collapse following fierce crying that suddenly stops with or without the clear cut breath holding phase, annotation will be made also. If there is a classical breath-holding-spell with no or very short white phase this event will be listed under faints as a separate group. Fainting in older children is also listed as a separate group within the category collapse. Just pallor or apathy or prolonged sleeping or limpness are not considered collapse reactions.
- Convulsions or Fits: all episodes with tonic and/or clonic muscle spasms and loss of consciousness. There is discrimination by body temperature in non-febrile and febrile convulsions: if fever is over 38.5°C it is booked as febrile convulsion unless the convulsion is symptomatic for meningitis or for other major illness. Febrile seizures of more than 15 minutes or asymmetrical or recurring within 24 hours are complex as opposed to simple. Definite epileptic phenomena are included in this category. A separate group under fits are the unspecifiable atypical attacks. These are paroxysmal occurrences without the specific criteria for collapse or convulsions. Nocturnal myoclonus is not included, neither are episodes of irritability, jitteriness; these are grouped under general illness.
- Encephalitis and Encephalopathy: children younger than 24 months with encephalopathy have an explicit or marked loss of consciousness for at least 24 hours which is not caused by intoxication and not explicable as post-ictal state. In children older than 24 months there must be at least 2 of the 3 following criteria must be fulfilled:
 - distinct change in mental status as disorientation, delirium or psychosis not caused by drugs;
 - marked decrease in consciousness not caused by seizures or medication;
 - seizures with (long lasting) loss of consciousness;
 Also signs of increased intracranial pressure might 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, are not included.
- Death: all reported children who died following immunisation are included in this category and not under one of the other listed categories.

Box 7. Main event categories with subdivisions according to severity

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

5.6 Recording, Filing and Feedback

Symptoms, (working) diagnosis and event category and assessed causal relation are recorded on the notification file together with all other information about the child, as medical history, discharge letters. Severe and other important events are discussed in the periodic clinical consultation 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. All the coding is done by a single physician 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 the selected cases to be re-evaluated by the GR committee. A project has been started for a database application which allows for both feedback and aggregated analysis. (see paragraph 5.8)

5.7 Health Council

Since 1984 Health Council (GR) advises the Minister of Health on the safety of the National Vaccination Programme. A permanent committee has been appointed. Currently this expert group includes specialists on the following different fields: paediatrics, child Health Care, public health, epidemiology, microbiology, neurology, immunology, pharmacovigilance, pathology, vaccinology. The safety advice is mainly based 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 the notifications without formal written assessment by LVO-RIVM, the final judgement on the safety of the programme is reached. Two

physicians of LVO-RIVM are advisory member of the GR committee. Annually, the GR committee makes a working visit to LVO-RIVM to audit the proper procedures and the completeness of registration and the quality of assessments.

Summarised reassessments of the GR committee are published in annual GR reports to the Minister of Health. Included are the AEFI which are reassessed in the working period of the committee. There is an inherent considerable and variable lag time between notification and this reassessment. Because the LVO-RIVM annual reports include all reported cases in a calendar year of which selected ones are included in the GR reports under responsibility of the committee, there is inevitable overlap. Numbers should thus not be added up.

Because the workload of the committee had to be diminished and assessment criteria have been agreed upon, only a selection of listed events are reassessed from 1996 onwards, with review of summarised reports of the other events. For the year under report (1995) this change in procedure did not have much impact; nearly all written assessments by LVO-RIVM were re-evaluated individually by the committee. The aggregated results were, however, all considered by the GR committee and this current report will be commented upon in their next annual advice to the Minister (1997). The first RIVM annual report on adverse events over 1994 has been appraised in the GR committee's advice of 1996.

5.8 Annual Reports and Aggregated Analysis

The coded forms are used as data sheets for the annual reports. For the current annual report all reported events have been recoded in one run by one of us (PEVdB), because the special code forms are only in use from mid 1997. Grouped events were checked for maximum consistency. Final diagnosis, causality and categorisation have been checked sample wise by independent double review by the two other physicians/investigators. Results were compared and showed remarkable consistency with virtually no inter-observer variability. None of the checked events needed recoding and they were categorised in the proper tables. The development of the database is behind schedule and the data for this report have not been entered in a database, therefore the analysis had to be done by hand. This is the main reason for the delay of this annual report. Trend analysis as planned and more in-depth evaluation 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 internal inspection and the GR audit over the year 1995. This visit will be commented upon in GR report 1997; The audit over 1994 is included in GR report 1996.

6. Results

6.1 Number of Reports

In 1995 LVO-RIVM received 796 notifications of adverse events on a total of over 2 million vaccinations. (birth cohort 191.905) The notifications involved 786 children because there were ten children with multiple reports, concerning two different vaccination dates. Four reports were compound with two distinct adverse events concerning one vaccination date. These are listed under the respective event categories. As described in paragraph 4.2, notifications of adverse events concerning more than one vaccination date with only mild or common symptoms were booked as single reports (Table 1). This annual report contains 800 reported adverse events.

Table 1. Types of reports of notifications of AEFI in 1995

notifications	children	adverse events
single	772	772
multiple	10	20
compound	4	8
total	786	800

Comparison of notifications with prior years is hampered, because only from 1994 onwards all incoming notifications are recorded in the logbook and get a file number according to year of notification. Before, only the more severe or particular events with formal written assessment were archived according to year of vaccination. The other reports were just put in store without listing. Even without exact counts of former years, it is clear that the number of reported events rises (Table 2). This increase seems to be continuing, at a slower pace, in 1996 and 1997. As in 1994 the notification rate is not even over the months, range 40-86, with the lowest rate in winter.

Table 2. Number of reported adverse events following immunisations (AEFI) per year

	written assessments*	total [#]
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

* before 1994 registration according to year of vaccination; from 1994 registration according to year of notification

[#] up till 1993 total numbers are estimates; from 1994 onwards totals are accurate counts

Criteria for formal written assessment changed in 1996; this may have had some influence on the year of report, with less written assessments.

6.2 Reporters

The first person to notify LVO-RIVM about an adverse event is regarded as the reporter. As in previous years the vast majority of reports were made by telephone. Only 27 notifications came by regular mail, even less than in 1994 (37); most frequently as (hospital discharge) letter, and some on regionally used, special report forms.

Reports from child health clinics accounted for over 80% of the total number with a rise of $\pm 15\%$ compared to 1994. The other notification sources were more or less stable (Table 3).

Table 3. Source and reporting route of AEFI in 1995

	1993	1994	1995	telephone	mail
Clinic staff Physician	341	474	548	535	13
Nurse	40	78	102	102	-
Paediatrician	54	60	59	48	11
General Practitioner	27	25	13	13	-
School Health Service	23	15	18	18	-
District Consultant	-	9	18	15	3
Parent	11	25	34	34	-
Other	-	5	6	6	-
Unknown	-	21	2	2	-
Total	496*	712	800	773	27

* estimate

The parents of 34 children reported directly themselves; mostly they were advised to do so by the clinic staff. Only once a notification came from a pharmacist and five times from PEA employees. On two registration forms the reporter was not noted.

6.3 Regional Distribution

Reports come from all over the country, but are not evenly spread. Standardisation of the rate per 1000 vaccinated infants shows that only three regions differ significantly from the country's average of 4.2/1000. Below average score Drenthe and Zeeland, and a little above, Amsterdam. This does not have very much impact in absolute numbers, since these area's do not have large populations per region. Compared to 1993 and 1994 the distribution over the country is more evenly in 1995. See table 4 and figure 1. Remarkable is the decrease in notification rate of Den Haag for the second year in a row.

Table 4. Regional distribution of reported AEFI in 1995, per 1000 vaccinated infants

	1993	1994	1995	95% c.i. #
Groningen	3.2	3.1	4.3	2.7-6.0
Friesland	1.2	2.5	4.7	3.2-6.3
Drenthe	1.1	1.8	2.0	0.8-3.2
Overijssel	1.9	2.1	4.0	2.9-5.0
Flevoland	0.5	1.4	3.4	1.7-5.1
Gelderland	1.6	2.9	4.0	3.2-4.8
Utrecht	3.5	4.6	4.2	3.2-5.3
Noord-Holland*	1.7	2.4	3.8	3.0-4.6
Amsterdam	4.7	8.2	6.0	4.3-7.7
Zuid-Holland*	3.3	4.6	5.0	4.2-5.8
Rotterdam	3.6	4.1	5.4	3.4-7.5
Den Haag	7.0	6.0	3.0	1.7-4.3
Zeeland	0.5	1.2	2.5	0.9-4.0
Noord-Brabant	2.4	3.3	3.7	3.0-4.4
Limburg	1.5	3.4	4.2	3.1-5.3
Netherlands @	2.6	3.6	4.2	3.9-4.5

proportionate confidence interval

* provinces without the three big cities

@ The Netherlands have a birth cohort of approximately 200.000 per year and coverage of 97% on average

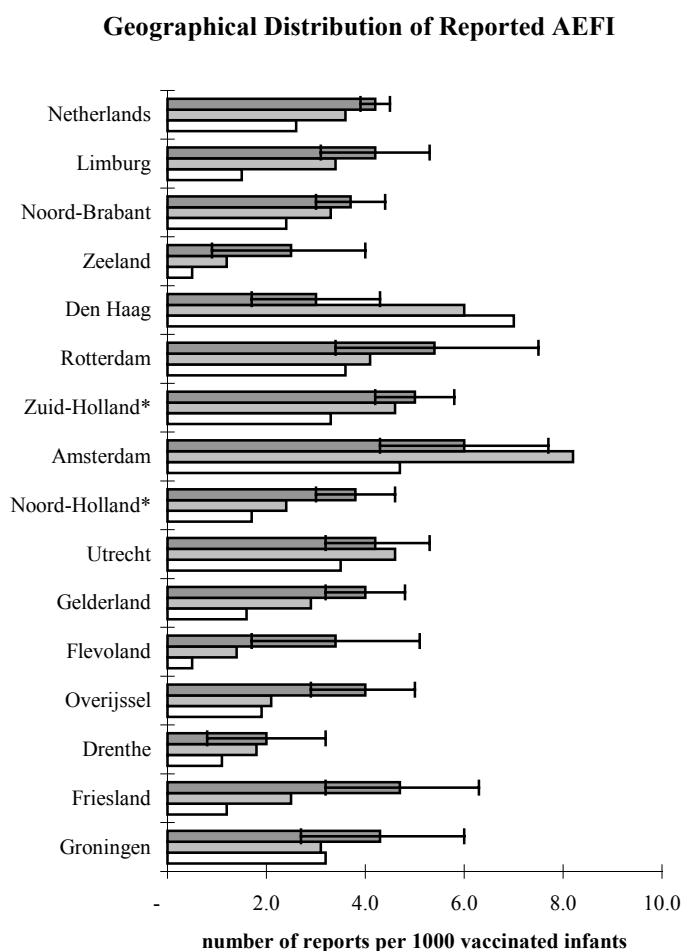


Figure 1. Number of reported AEFI in 1995 per 1000 vaccinated infants

6.4 Vaccines

In 1995, most notifications were about recent vaccinations, 671 (+ 34 of which the exact date was unknown) in 1995 and 83 in 1994. Two reports involved vaccinations in 1993. Four reports were about earlier vaccinations, in 1985, 1987 and 1988.

As in 1994, reports on the first DTP/Hib vaccinations were the most prevalent (324), with declining numbers on subsequent doses and older age, respectively 141, 103, 83 for second, third and fourth dose (Table 5). Only 21 times no Hib was given simultaneously with DTP. Two reports concerned HB vaccine, once given together with DTP and once with DTP and Hib. Six children received DTP instead of the scheduled DTP. Two of them because of prior adverse events, twice because of perceived contra-indications and two parents refused pertussis vaccine altogether, once Hib also, on philosophical grounds.

MMR was involved 114 times; MMR-1, 96 times, in eight cases with simultaneous other vaccines, in one child at the age of four years with DTP-5. MMR-2 was involved 18 times, all but once with simultaneous DTP-6.

The revaccination at 4 and 9 years were involved only 18 and 21 times respectively.

Table 5. *Schedule and vaccines of reported AEFI in 1995*

vaccine	given⇒	dtp	dtp hib	dtp hib mmr	dtp mmr	mmr	mmr hib	dtp	dtp hib	dtp mmr	dtp hib mmr	hib	bcg	total	
scheduled ↓														1995	1994
dtp-1+hib-1		9*	313*	-	-	-	-	1	1	-	-	-	-	324	300
dtp-2+hib-2		6 ^{&}	134	-	-	-	-	-	1	-	-	-	-	141	126
dtp-3+hib-3		3	97	-	-	-	-	1	1	-	-	1	-	103	91
dtp-4+hib-4		2	81	-	-	-	-	-	-	-	-	-	-	83	70
dtp-?+hib-?		1	8	-	-	-	-	-	-	-	-	-	-	9	2
mmr-1		-	-	4	2	87	1	-	-	-	1	-	-	95	74
dtp-5		-	-	-	-	-	-	17 [@]	-	1	-	-	-	18	11
dtp-6+mmr-2		-	-	-	-	1	-	3 [@]	-	17 ^x	-	-	-	21	21
hib catch-up		-	-	-	-	-	-	-	-	-	-	3 ^{\$}	-	3	8
other		-	-	-	-	-	-	-	-	-	-	-	3	3	9
total		21	633	4	2	88	1	22	3	18	1	4	3	800	712

* once plus HepB vaccine first dose DTP and first dose DTP/Hib

& one time catch up dose in 2.8 years old child in refugee asylum

@ one time first catch up dose at ages 4 and 8 years

x twice first catch up dose in refugee asylum

\$ one time non programme Hib vaccine in older child

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. Convulsions, especially febrile, are reported more often after the fourth DTP/Hib and the first MMR. See for details the paragraphs of the specific event categories (Paragraph 6.9).

No children with anaphylactic shock were reported. One child reported in 1994 had possible anaphylactic shock more than 24 hours after the vaccination and within 15 minutes of ingesting newly introduced food; this child was listed under major illness, and further vaccinations were uneventful.

Table 6. *Event category and (scheduled) vaccine dose of reported AEFI in 1995*

event ↓	vaccine⇒*	dtp first	dtp second	+ third	hib fourth	mmr-1 dose?	dtp-5	mmr-2 dtp-6	hib catch-up	bcg	total	
											1995	1994
local reaction		7	7	1	8	1	3	2	4	3	39	31
general illness	minor	102	54	46	27	3	33	6	9	-	280	242
	major	13	14	7	9	1	9	1	1	-	55	61
persistent screaming		14	3	5	-	-	-	-	-	-	22	37
skin symptoms		18	6	8	6	2	17	3	1	-	61	78
discoloured legs		55	22	10	3	2	-	1	-	-	93	43
faints		102	24	10	2	-	-	5	4	-	147	141
fits		11	10	14	28	-	32	-	2	-	97	74
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		-	-	-	-	-	1	-	-	-	1	-
death		2	1	2	-	-	-	-	-	-	5	5
total		324	141	103	83	9	95	18	21	3	800	712

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

In the numbers in the tables all reported events are included irrespective of causality. See for degree of causality, Paragraph 6.8, and the specific events under Paragraphs 6.9.

6.5 Feedback to Reporters

Feedback of diagnosis and causality with advice about further vaccinations is a major characteristic of the surveillance system. This feedback is most often by telephone; 30% of reports got a full written account (Table 7).

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

event ↓	feedback method ⇒	written	telephone	total
local reaction		5	34	39
general illness	minor	59	221	280
	major	25	30	55
persistent screaming		3	19	22
skin symptoms		9	52	61
discoloured legs		13	80	93
faints		56	91	147
fits		58	39	97
anaphylactic shock		-	-	-
encephalopathy/-itis		1	-	1
death		5	-	5
total		234	559	800

6.6 Source of Information and Medical Intervention

In a little over half the notifications the reporter was the sole informant, in 47% information was received from others also (Table 8). In 90% of reports the clinics (child Health Care, school health and refugee clinics) supplied information. Parents were in more than 40% of cases contacted and sole informer of 13 reports. Information was supplied by hospital specialists in 17% of reports.

Table 8. *Information sources and events of reported AEFI 1995*

info ⇒	clinic	parent	gp	hospital	other	unknown	total
event ↓	+	+	+	+	+	+	776
local reaction	-	+	+	+	+	+	341
general illness	-	-	-	+	+	+	42
persistent screaming	-	-	+	+	+	+	139
skin symptoms	-	-	-	-	-	+	2
discoloured legs	-	-	-	-	-	-	2
faints	27	5	2	-	1	1	39
fits	161	82	14	5	2	5	280
anaphylactic shock	24	13	8	-	3	5	55
encephalopathy/-itis	16	5	-	-	-	-	22
death	34	13	3	3	1	2	61
total	65	21	4	-	1	-	93
local reaction	57	61	20	2	2	4	147
general illness	22	18	27	6	4	13	97
persistent screaming	-	-	-	-	-	-	-
skin symptoms	-	-	-	-	-	1	1
discoloured legs	-	-	-	-	-	-	-
faints	-	-	-	-	-	1	1
fits	-	-	-	-	-	-	-
anaphylactic shock	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	-	-	1	1
death	-	-	1	-	1	2	5
total	406	218	79	16	14	33	800

The impact of adverse events may also be illustrated by medical intervention received. In 47% of reported events no professional medical help was sought or was not recorded by us. 66 Parents administered paracetamol suppositories or, once, diazepam by rectiole. In more than half of the events (53%) parents contacted the clinic, GP, the ambulance, or hospital, with a little over 10% admittance. In Table 9 intervention is ordered according to highest level used.

Table 9. Medical intervention and events of reported AEFI in 1995

event↓ intervention→	?	none [#]	supp [*]	clinic [@]	gp tel [§]	gp visit ^{&}	ambu lance ^x	out- patient	emerg ency	hospital stay	other	post mortem	total
local reaction	23	3	1	4	1	3	-	1	-	3	-	-	39
general illness minor	100	37	30	7	15	57	-	20	1	12	1	-	280
major	14	1	5	-	7	11	-	4	-	13	-	-	55
persistent screaming	15	-	3	-	2	2	-	-	-	-	-	-	22
skin symptoms	13	5	2	7	3	22	-	5	1	3	-	-	61
discoloured legs	25	8	17	15	5	15	-	4	1	2	1	-	93
faints	13	35	7	9	8	43	1	8	4	19	-	-	147
fits	15	4	1	1	3	19	6	5	6	37	-	-	97
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	-	-	-	-	-	-	1	-	-	1
death	-	1	-	-	-	-	-	-	-	1	-	3	5
total	218	94	66	43	44	172	7	47	13	90	2	3	800

[#] homeopathic or herb remedies, baby massage or lemon socks are included in this group, as are cool sponging.

^{*} apart from paracetamol suppositories, stesolid rectioles and other prescribed or over the counter drugs are included

[@] telephone call or special visit to the clinic

[§] consultation of general practitioner by telephone

[&] examination by general practitioner

^x ambulance call and visit without transport to hospital

6.7 Sex Distribution

Overall more boys (56%) were reported than girls although a little lower percentage than in 1994 (60%). Distribution over the different events ranged from 48% boys (atypical attacks) to 66% in local reactions with the events with less than 10 reports excluded. See for specifics on the events and subdivision, the respective categories under paragraph 6.9.

Under unknown are several cluster reports of minor illness, local reactions and fainting.

Table 10. Events and sex of reported AEFI in 1995

event ↓ sex→	male	female	unknown	total
local reaction	23	12	4	39
general illness minor	152	116	12	280
major	27	27	1	55
persistent screaming	10	11	1	22
skin symptoms	30	29	2	61
discoloured legs	49	42	2	93
faints collapse	84	53	-	137
BHS	-	2	-	2
fainting	-	5	3	8
fits convulsions	38	26	-	64
epilepsy	2	1	-	3
atypical attacks	13	15	2	30
anaphylactic shock	-	-	-	-
encephalopathy/-itis	1	-	-	1
death	4	1	-	5
total	433	340	27	800

6.8 Causal Relation

Adverse reactions are events with (likelihood of) causality assessed as certain, probable or possible. In 1995 that was the case in 81% of reports. The other events were considered coincidental events with

improbable or absent causal relation with the vaccinations. Only eight notifications were not classifiable. There are great differences over the event categories, in this respect, with on the one end persistent screaming for 100% a more or less likely causality and on the other extreme the children who died, where there was no causal relation with the vaccinations in all instances. For MMR vaccination only 54% of reported adverse events were considered an adverse reaction. For DTP, DTPP and Hib vaccinations this percentage was nearly 86. See for further specifics the event categories below (Paragraph 6.9).

In 1994 84% of reports were regarded adverse reaction.

Table 11. Causality and events of reported AEFI in 1995

event ↓	causality⇒	certain	probable	possible	improbable	non classifiable	total
local reaction		27	4	5	-	3	39
general illness	minor	-	121	93	64	2	280
	major	-	19	11	25	-	55
persistent screaming		-	22	-	-	-	22
skin symptoms		-	4	24	31	2	61
discoloured legs		-	87	3	2	1	93
faints	collapse	-	121	13	3	-	137
	BHS	-	1	1	0	-	2
	fainting	-	6	1	1	-	8
fits	convulsions	-	17	43	4	-	64
	epilepsy	-	-	-	3	-	3
	atypical attacks	-	1	17	12	-	30
anaphylactic shock		-	-	-	-	-	-
encephalopathy/-itis		-	-	-	1	-	1
death		-	-	-	5	-	5
total		27	403	211	151	8	800

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 1995.

6.9.1 Local reactions

39 Reported cases had predominant local symptoms, mostly after simultaneous DTPP/ Hib vaccinations and quite often at both sites. Three reports were not classifiable mainly because of incomplete notifications and lacking data on time interval and exact site; twice this concerned BCG vaccination with local hair growth and once a cluster report about Hib. All other reports were considered adverse reactions (Table 10). Most often the symptoms were common local inflammation, six times severe or prolonged. Three children had pain, at the injection site, only. The two children with abscess were culture positive (*β* haemolytic streptococcus A). No faulty procedures were involved in these cases. The so called atypical local symptoms were discoloration of the skin, pigmentation/depigmentation, scar tissue, hair growth, etceteras (Table 12).

Table 12. *Local reactions and vaccines of reported AEFI in 1995*

vaccine⇒ event↓	dtp/hib1	dtp/hib2	dtp/hib3	dtp/hib4	dtp/hib?	dtp/mmr1	mmr1	dtp5	dtp6/mmr2	hib	bcg	total
mild/moderate	2	2*	-	2 ^{\$}	1 ^{\$}	1	1	-	2	1 ^{\$}	1	13
severe/prolonged	1	1	1*	1	-	-	-	1	1 [^]	-	-	6
pain	-	-	-	3	-	-	-	-	-	-	-	3
abcess	1	-	-	1	-	-	-	-	-	-	-	2
atypical	3	4	-	1	-	-	1	1	1	2	2	15
total	7	7	1	8	1	1	2	2	4	3	3	39

* once dtp only

[^] once first catch up dose refugee^{\$} one time cluster report

MMR was involved seven times; of the five times MMR was given simultaneously with D(P)TP, once complaints were at either injection site and once there was a haematoma at the MMR site. In the other three reports symptoms were at the injection site of D(P)TP.

6.9.2 Systemic symptoms

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

6.9.2.1 *general minor illness*

Of 280 children the complaints were considered minor illness, in 23% with no causal relation with the vaccination (in 1994 17%) (see also Table 11). 83% of reports concerned the scheduled DPTP/Hib vaccinations with the majority of events following the first vaccinations with DPTP/Hib. (Table 13) For comparison the numbers of 1994 are included. Only very few times it was possible to make a definite diagnosis, mostly working diagnoses were used. These are listed in Table 14 with the most pronounced second symptom also summarised. Fever was the most frequent main symptom (86), three times only low grade, and also the most frequent second symptom. The five reports with prolonged fever were not considered serious events (per se). Crying was the second most frequent main symptom (30), 18 times fierce, 11 times screaming and once prolonged. Twice as often crying was the most pronounced accompanying symptom. Irritability was quite frequently diagnosed, as were chills and (sleeping) jerks, with or without fever. Pallor as sole symptom was quite frequent as well, as were gastro intestinal complaints. Like other years there were a few children with bulging fontanel, a couple in this category and another one was grouped under major illness. Also a couple of children with red urine (myoglobinuria?) are included in the minor illness category. See for further symptoms table 14.

Table 13. *Minor illness and vaccines of reported AEFI in 1995*

scheduled vaccine ↓	1995	1994
dtp/hib1 @	102	104
dtp/hib2 #	54	53
dtp/hib3 \$	46	37
dtp/hib4	27	13
dtp/hib?	3	?
dtp/hib/mmr1	2	?
mmr1	31	20
dtp5	6	3
dtp6/mmr2 &	9	5
other	-	7
total	280	242

@ once only dtp, once only dtp, once dtp+hbv, once dtp+hib+hbv

twice only dtp

\$ twice only dtp, once dtp+hib

& twice only dtp and once only mmr

Of the 40 times MMR was administered, either singly (32) or simultaneously (8) with other vaccines, the MMR vaccine was implicated 18 times or 45% . (crying-1, vaccinitis-5, irritable-1, fever-5, parotitis-1, swollen cheek-2, vomiting-1, swollen groin-1, asthma attack-1). The symptoms were likely to have been caused by the simultaneous DTP/Hib (irritable) once. The others were considered to be coincidental events. Thus with MMR less than half of the reports in the category were considered possible side effects. For the other vaccines listed, this was approximately 82%.

Table 14. Main (working) diagnosis or symptoms in minor illness of reported AEFI in 1995

symptom or diagnosis	main	second	total	symptom or diagnosis	main	second	total
fever	86	121	207	pallor	23	23	46
crying	30	61	91	cyanosis	1	5	6
irritability	10	15	25	icterus	1	-	1
meningismus	2	-	2	flush	1	-	1
myoclonics	22	8	30	rash illness	10	16	26
chills	15	3	18	vaccinitis	5	-	5
bulging fontanel	2	-	2	chickenpox	1	-	1
asthma attack	3	-	3	shingles	1	-	1
airway infection	9	5	14	parotitis	2	-	2
apnoea	1	3	4	swollen cheek	2	-	2
groaning	1	5	6	swollen limbs	1	-	1
listlessness	6	1	7	lymphadenopathy	1	-	1
drowsiness	3	10	13	eczema	1	-	1
prolonged sleeping	4	7	11	stomatitis	1	-	1
restlessness	4	7	11	feeding difficulty	1	4	5
pain in limbs/muscles	2	-	2	vomiting	7	12	19
lying still/frozen	3	-	3	diarrhoea	3	-	3
limpness	1	1	2	gastro-enteritis	4	-	4
rolling eyes	2	6	8	swollen groin	1	-	1
nystagmus	1	-	1	torsio testis	1	-	1
ptosis	1	-	1	myoglobinuria?	3	-	3
?	1		1				

6.9.2.2 major general illness

55 reports were classified as major general illness, a little less than in 1994 (61). High fever of $\geq 40.5^{\circ}\text{C}$ was the main feature in 35 cases in this category. Not included are high fevers as parts of a distinct disease or with convulsion (Table 15). The five reports with prolonged fever were not considered major per se in contrast to 1994, and are listed under minor illness. The distribution is more even over the scheduled vaccines than in the minor illness group. For causality see table 16. MMR was involved 11 times, twice given simultaneously with DTP5 or 6. Four times the MMR vaccination was considered the possible cause of high fever (3) and idiopathic thrombocytopenic purpura (ITP) (1). In this last case, concurrent viral intestinal infection and upper airway infection could have been the cause as well. The other time ITP followed MMR, it was caused by natural rubella infection occurring just prior to vaccination: MMR vaccination had been postponed because of rash and splenomegaly a few weeks earlier. Both children recovered without complications. The remaining six events after MMR vaccinations were considered coincidental because of time interval or established other cause. Transient erythroblastopenia of childhood (TEC) appeared to be caused by Epstein Bar Virus infection and in the child with nephrotic syndrome the time interval with vaccination was too short, as was the case in the child with septic arthritis.

Table 15. Major illness and vaccines of reported AEFI in 1995

diagnosis↓	vaccine⇒	dtp/hib1	dtp/hib2	dtp/hib3	dtp/hib4	dtp?	mmr1	dtp6/mmr2	total
high fever		11	8	4	8	-	4	-	35
metabolic disease		-	-	-	1	-	-	-	1
bronchiolitis		-	-	1	-	-	-	-	1
apnea		1	-	-	-	-	-	-	1
pneumonia		-	1	-	-	-	-	-	1
exanthema subitum		-	-	1	-	-	-	-	1
meningitis		1	3\$	-	-	-	-	-	4
sepsis		-	1	-	-	-	-	-	1
bulging fontanel		1	-	-	-	-	-	-	1
TEC		-	-	-	-	-	1	-	1
ITP		-	-	-	-	-	2#	-	2
nephrotic syndrome		-	-	-	-	-	1	-	1
rotavirus infection		-	-	-	-	-	1	-	1
septic arthritis		-	-	-	-	-	1	-	1
autism		-	-	-	-	1	-	-	1
photophobia / chickenpox scar		-	-	1	-	-	-	-	1
Gilles de la Tourette		-	-	-	-	-	-	1	1
total		14	13	7	9	1	10	1	55

once mmr1 was given with dtp5

\$ twice only dtp (vaccinations in 1988 and 1985)

Of the events following (scheduled) DTP/Hib vaccinations 26 out of 44 events were possibly or probably vaccine caused or potentiated. For the other events different causes have been established satisfactorily, like RSV infection, sixth disease, metabolic disorder. The sepsis was caused by campylobacter infection.

Table 16. Major illness and causal relation of reported AEFI in 1995

diagnosis ↓	causality⇒	certain	probable	possible	improbable	unclassifiable	total
high fever		-	19	9	7	-	35
metabolic disease		-	-	-	1	-	1
bronchiolitis		-	-	-	1	-	1
apnoea		-	-	-	1	-	1
pneumonia		-	-	-	1	-	1
exanthema subitum		-	-	-	1	-	1
meningitis		-	-	-	4	-	4
sepsis		-	-	-	1	-	1
bulging fontanel		-	-	1	-	-	1
TEC		-	-	-	1	-	1
ITP		-	-	1	1	-	2
nephrotic syndrome		-	-	-	1	-	1
rotavirus infection		-	-	-	1	-	1
septic arthritis		-	-	-	1	-	1
autism		-	-	-	1	-	1
photophobia / chickenpox scar		-	-	-	1	-	1
Gilles de la Tourette		-	-	-	1	-	1
total		-	19	11	25	0	55

The four meningitis cases all had an inconceivable time interval. Once the cause was probably viral and in the other three, bacterial (Hib, *Streptococcus pneumoniae* and culture negative/undetermined). The latter child recovered but died 6,5 weeks after the subsequent DTP/Hib vaccination (paragraph 6.10).

6.9.3 Persistent Screaming

Compared to 1994 less children were reported with persistent screaming (22 vs 37). One child with discoloured legs (see below) and possible persistent screaming is not included. In eight cases there

was also fever on the day of vaccination. As was noticed in former years this reported adverse event seems age/dose dependent (see table 6 and 13). Local symptoms were pronounced in only five cases, of which two only had (presumed) pain at the injection site and no other signs of inflammation. A couple of children had both sided local reaction. Additional symptoms were restlessness, change in sleeping behaviour, pallor, vomiting, eye turning and thrashing about. Parents were usually desperate but only four seem to have contacted the family physician. We did not record the degree of intervention in the majority of cases, however.

In all children there was a possible or probable likelihood that the vaccination was causally related with the event.

6.9.4 General skin manifestations/phenomenon

Skin symptoms were the main or only feature in 61 reports. Discoloured legs are not included but categorised separately (see below). The child with petechiae listed here, had them on face and arms while vaccinated in both legs. The distribution over the different vaccine doses is rather evenly except for rash after the first DPTP/Hib. 18 cases concerned MMR, twice together with DPTP and once with simultaneous DTP (Table 18).

Table 17. Skin symptoms and vaccines of reported AEFI in 1995

vaccine⇒ symptoms↓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dptp/hib?	mmr1	dptp/mmr1	dp5	dp6/mmr2	total
angio-edema	2	1 \$	-	2 \$	-	2	-	-	-	7
vesicles	1	-	-	-	-	1	-	-	-	2
exanthema	8 #	1	2	1	2	6	-	-	1	21
impetigo	-	1	-	-	-	1	-	1	-	3
harlequin	2	-	-	-	-	-	-	-	-	2
urticaria	3	3	2	3	-	5	2	2	-	20
eczema	1	-	1	-	-	-	-	-	-	2
erysipelas	-	-	1	-	-	-	-	-	-	1
acra pallor	1	-	-	-	-	-	-	-	-	1
cutis marmorata	-	-	1	-	-	-	-	-	-	1
petechiae	-	-	1	-	-	-	-	-	-	1
total	18	6	8	6	2	15	2	3	1	61

1x dptp only

\$ 1x dtp/hib

Overall less than half the reports (47%) were considered causally related with the vaccination (Table 11). For MMR, given separately 15 times and twice with DPTP and once with DTP, causality was inferred in six reports (33%) only (urticaria 1x, exanthema 3x, angio-oedema 2x); the time interval in these cases is crucially important. In one of the other reports there was very mild fever and rash in the appropriate interval for MMR vaccination, but this was not listed under minor illness, since these complaints were not the reason for notification and the reported other skin symptoms were much more striking, but not causally related, however. The category minor illness includes another five reports of children in which “vaccinitis” was the only event. Under major illness another child with high fever and some rash, but also upper airway symptoms; this report is listed under high fever.

Table 18. Skin symptoms and causal relation of reported AEFI in 1995

causality⇒ symptom⇓	certain	probable	possible	improbable	unclassifiable	total
angio-oedema	-	1	3	2	1	7
vesicles	-	-	-	2	-	2
exanthema	-	1	11	9	-	21
impetigo	-	-	-	3	-	3
harlequin	-	1	1	-	-	2
urticaria	-	-	7	12	1	20
eczema	-	-	1	1	-	2
erysipelas	-	-	-	1	-	1
acra pallor	-	-	1	-	-	1
cutis marmorata	-	1	-	-	-	1
petechiae	-	-	-	1	-	1
total	-	4	24	31	2	61

6.9.5 Discoloured legs

Starting this year, a separate category are discoloured legs. These are subdivided in blue, red or purple legs with diffuse or patchy discoloration, with or without petechial rash. Leg petechiae without noted discoloration are also grouped in this category. Descriptive epidemiology and follow up of these reports will be reported separately.

A total of 93 reports came in of which 21 were blue legs (18 double sided), 47 red legs (34 double sided). The 19 purple legs were mostly patchy (15 double sided). Of the 23 one sided discoloration's half were on the Hib leg and half on DPTP leg, with three cases unknown. In total, 18 children had petechiae, including six reports without noted prior discoloration of the legs; 11 times double sided and nine times one sided of which seven times on the Hib side, once on the DPTP side and once unknown (Table 19).

About one quart of the children had also fever and one child had $\geq 40.5^{\circ}\text{C}$. Over half the children exhibited fierce crying of whom 6 for several hours (once possibly persistent screaming). Injection site reactions, if any, were not pronounced.

Four of the reports were compound, with three times also collapse and once also convulsion. These reports are grouped under collapse and convulsion as well.

Reports of discoloured legs were most frequent after the first DPTP/Hib vaccinations and decreasing in number with dose/age. The report after DTP5 concerned a child with a purple arm, from armpit to fingers with the vaccine administered in the upper arm.

Causal relation with the vaccine was inferred in all but three cases (once unclassifiable). See table 11.

Table 19. Discoloured legs and vaccines of reported AEFI in 1995.

symptoms⇓ vaccine⇒	dtp/hib1	dtp/hib2	dtp/hib3	dtp/hib4	dtp/hib?	dtp	petechiae	total
blue legs	16 #	4	1	-	-	-	-	21
red legs	29 ^	12	2	2 *	2	-	9	47
purple legs	9	4	4	1	0	1	5	19
petechiae only	1	2	3	-	-	-	6	6
total	55	22	10	3	2	1	20	93

twice also collapse reaction

^ once also collapse reaction

* once also convulsion

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

6.9.6 Faints

In this event category collapse (hypotonic-hyporesponsive episode, HHE), syncope (fainting) and breath-holding-spells (BHS) are listed (Table 20). The collapse cases of this year have had some special attention. All children with collapse reported after the first vaccination have been followed and were studied in a case-control design. This study will be reported separately (Collapse reactions following vaccinations under the National Vaccination Programme of the Netherlands; part I, descriptive epidemiology and part II, follow up and case control study- in preparation).

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.

Two children had breath-holding-spells with turning blue, after stopping to breath in expiration when fiercefull crying, with very short phase of diminished responsiveness, no limpness or pallor. Another child had apnoea straight after the first injection; this child suffered from the congenital Joubert syndrome with an abnormal breathing pattern and frequent apnoea on different stimuli. This report is listed under major illness.

There were eight reports of fainting, of which three were cluster reports of nine year olds.

Table 20. *Faints and vaccines of reported AEFI in 1995*

event↓ vaccine⇒	dtp/hib1	dtp/hib2	dtp/hib3	dtp/hib4	dtp5	dtp6/mmr2	total
collapse	100@	24#	10 \$	2	1	-	137
breath holding spell	2 *	-	-	-	-	-	2
fainting	-	-	-	-	4	4^	8
total	102	24	10	2	5	4	147

* once dtp/hib

@ once with simultaneous hbv and three times only dtp and once dtp

once dtp only in refugee child of 2.8 years

\$ once only hib

^ 3 cluster reports

Only three cases of collapse were not regarded adverse reactions, with improbable causal relation; once after DPTP/Hib1 and -2 and once after Hib3 vaccination, because of inconceivable interval. Of the fainters, one cluster report, of class mates, more than a day after vaccination and gastro intestinal complaints, was also seen as chance occurrence. See also table 11 and table 10 for sex distribution.

Of the collapse cases, only 22 children developed fever on the day of the incident, once $\geq 40.5^{\circ}\text{C}$, but only two children had fever at the time of the incident.

6.9.7 Fits

In this category (febrile) convulsions and epileptic seizures find a place. Also atypical attacks in case a definite diagnosis could not be made and convulsion could not be excluded either, are listed here. Most convulsions were accompanied by fever, occurring predominantly after the fourth DPTP/Hib and MMR1 vaccinations. The non-febrile convulsions are more evenly distributed over the different doses; the atypical attacks tended to be most frequent in the first half year of life (Table 21). Fits at the younger ages were less frequently accompanied by fever than at the later doses/older ages, more so in case of convulsions than in the atypical attacks (Table 22). Altogether 14 children had fever of over 40.5°C .

Table 21. *Fits and vaccines of reported AEFI in 1995.*

event ↓	vaccine⇒	dtp/hib1	dtp/hib2	dtp/hib3	dtp/hib4	dtp/hib+mmr	mmr1	dtp6/mmr2	total 1995 1994	
febrile convulsion	simple	-	1	1	12	-	9	-	23	27
	complex	-	1	-	7\$	2*	8	-	18	20
	tonic	1	-	1	4	-	4	-	10	n.r
	atypical	2	1	-	2	-	2	-	7	3
afebrile convulsion		1	1\$	2	1\$	-	1	-	6	5
epilepsy			1	-	-	-	1	1#	3	3
atypical attack		7&	5	10@	2	-	5	1	30	16
total		11	10	14	28	2	30	2	97	74

* once dtp/hib/mmr and once dtp/mmr

once first catch up dose dtp only in eight year old

\$ once only dtp administered.

& twice only dtp

@ once dtp only

n.r not registered separately

Table 22. *Fits and fever of reported AEFI in 1995.*

event⇒ vaccine # ↓	convulsions*		atypical attacks	
	<38.5°C	≥38.5°C	<38.5°C	≥38.5°C
dtp/hib1	1	3 \$	5	2
dtp/hib2	2	3	1	4
dtp/hib3	2	2	6	4
dtp/hib4	1	25	-	2
dtp/hib+mmr	-	2		
mmr1	2	23 \$	-	5
dtp6	1	-	1	-
total	9	58	13	17

* afebrile/febrile and epileptic seizures

scheduled vaccines, for more specifics see table 21

\$ once with borderline fever

Boys are over represented in (febrile) convulsions; in atypical attacks distribution over the sexes is equal (see Paragraph 6.8, Table 10).

Altogether 81.5% of events in this category were considered to be possibly or probably causally related with the vaccination. Over 94% of convulsions were judged to be adverse reactions and 60% of the atypical attacks. None of the reported epilepsy's were regarded as caused by the vaccination (Table 11).

MMR was involved in 33 reports. In 30 cases as single vaccine, with inferred causal relation in 26. Three times MMR was given in combination with DTP4/Hib, DPTP4 or DTP6, with only once the event possibly caused by the MMR vaccine.

6.9.8 Encephalopathy/encephalitis

In 1995 there was one report of encephalitis. The boy received MMR and a catch up Hib vaccine at the age of 1.9 years in 1994. Three and a half weeks later he had an upper airway infection with cough and fever. A week and a half after he was hospitalised with encephalitis, probably of viral origin. He was treated with aciclovir and antibiotics. He recovered fully. No definite cause could be established. Causal relation with the vaccination was considered unlikely.

6.9.9 Anaphylactic shock

No cases were reported in 1995. In matter of fact, we never received notification of anaphylactic shock with inferred causality and/or appropriate time interval, since the surveillance system was installed.

6.9.10 Death

In 1995 five notifications came in of children who died after a vaccination of the RVP (Table 22). There were four boys and one girl. In none of the cases the events were considered to be caused or aggravated by the vaccine, nor was there an undue delay in diagnosis or therapy because of the vaccination.

Table 23. *Death and vaccines of reported AEFI in 1995.*

child	sex	age	vaccines	time interval		symptoms/diagnosis	causality	autopsy
				illness	death			
A	female	5 months	dtp/hib2	8 days	15 days	rota diarrhoea, dehydration; cerebral edema	no	yes
B	male	9 months	dtp/hib3	6.5 wks	6.5 wks	purpura fulminans, meningococcus B	no	yes
C	male	5 months	dtp/hib3	3.5 days	7 days	purpura fulminans, meningococcus B	no	no
D	male	3 months	dtp/hib1	8 days	8 days	sids	no	yes
E	male	3 months	dtp/hib1	36 hours	36 hours	clinical sids	no	no

Child A was a five month old girl who developed a rash eight days after the second DTP/Hib vaccinations. She was seen in hospital and two days later she got fever and diarrhoea and was hospitalised the next day because of dehydration. Rota virus was isolated from the stool. She was treated with I.V. rehydration. After initial improvement there was a sudden deterioration with convulsions and cerebral oedema. She died 15 days after the vaccinations. (The vaccinations had been postponed because of intercurrent illness one month before.)

Child B was a 10 month old boy who died within one day of the first signs of illness because of meningococcal septicaemia (serogroup B). Six weeks before he received his third DTP/Hib vaccinations, with a delay because of bacterial meningitis (culture negative) seven weeks after his second vaccinations.

Child C received his third vaccinations at the age of five months. Like after the previous doses he developed fever and cried more for one day. The following two days were uneventful until the fourth night when he woke up with a slight cold and a heat-rash-like discoloration in the waist area. After some time he was put back to bed and fell asleep again. The next morning there was difficulty in awakening him and there were a few petechiae on the abdomen. In hospital he was already in deep shock. He died because of irreversible damage to brain and extremities.

Additional investigations showed Fcγ receptor polymorphism with increased risk of severe bacterial infections. Counter-Immuno-Electrophoresis on a saved sample of cerebrospinal fluid was positive for Meningococcus (serogroup B).

Child D was a boy of three months old who was a little restless on the day of his first DTP/Hib vaccinations with a maximum temperature of 37.5°C. There have been no problems until a week later when he died 20 minutes after he had been put to sleep at the day-care centre. Autopsy revealed no abnormalities.

Child E, a boy of three month old, had no symptoms following his first DTP/Hib vaccinations. A day and a half later, when visiting friends, he was put to sleep in a “camping” bed together with his twin sister. After two hours he cried shortly, he was taken out and after quieting down put back again. Two hours later he was found dead, turned on his stomach with his face down. Autopsy was refused because of faulty information to the parents that the child could not be taken home first.

7. Discussion

Safety of the RVP is guarded by an enhanced passive surveillance system. The exact number of vaccinations is known, because of the registration by the PEA of all vaccines administered on individual level.¹⁶ The RVP is embedded in regular child Health Care with near total coverage, so the programme is delivered by a relative small group of specifically trained professionals. This is also advantageous for safety surveillance. The existence of a 24 h central telephone information service is a most important tool in acquiring notifications and makes very efficient use of resources both on the reporters' end as on the receiving end. The location of this safety surveillance system at RIVM with its available expertise should guarantee that the surveillance is of high quality.

But the Achilles' heel of passive surveillance is underreporting. Especially selective underreporting is of crucial importance. Whether or not the here presented data on reported AEFI are representative will be discussed.

7.1 Increase in Number of Reports

There appears to be a steady increase in numbers of reported AEFI, although numbers should be interpreted with caution since they are estimates and not counts up till 1993. But nevertheless there seems to be an actual increase. In 1987 and 1993 vaccines have been added to the programme and it is to be expected, even if they are administered simultaneously with existing vaccines, that there is a rise in true adverse reactions as well as a rise reported events that are coincidental but regarded as possibly related with the new and yet unknown vaccines. Reporting criteria have not been changed over the years, but awareness of the professionals and the public has increased lately, not only by the publicity around the newly introduced vaccines. Recently the need for vaccinations and the safety have been questioned in certain groups in the population and the public awareness of the severity of the target diseases has diminished now that the illnesses are effectively prevented by the vaccinations; this does increase the relative importance of side effects. This may influence the willingness to report possible adverse reactions as well. The rise in notifications is due to more reports from child health clinic staff, with a rise in reports from parents as well, although low in absolute numbers. The distribution over the different vaccine(dose)s and over the different event categories is similar to 1994 (table 5 and 6). Only the newly introduced category of discoloured legs stands out. We will discuss that under paragraph 7.8.2. There are no signs that the rise in number of notifications of AEFI is due to an actual rise in vaccine related events, but it is more likely (as in 1994) due to a further decrease in underreporting (see paragraph 7.3 below).

7.2 Reporting Route

As in former years, the majority of notifications is by telephone. This is of great advantage because a substantial part of the reports are posed as a question or spring from the need of advice, also in case of the more severe events, even with inferred causality. Reporters tell us that for them the reporting by telephone is less time consuming, and they appreciate the availability of direct consultation. We fear that with dividing this system in two, with reporting address and consultation service separated, will result in a tremendous loss of reports as well as in the quality of the reports. Moreover it will cost more resources because of less efficiency and/or it will mean loss of expertise and quality of the services. Unfavourable experience in other countries should be taken to heart (for instance Denmark and Canada and Sweden).¹⁷

Reporting by telephone has an additional advantage; it possesses the opportunity to clarify some of the data and to get some necessary additional information. The events reported by mail, whether discharge letters or report forms, are never complete enough to allow accurate diagnosis and causality assessment straight away. The quality of data is very diverse and often there is only a pre-interpreted diagnosis without noting the accurate symptoms involved. We always need to get further information, and contacting the reporter and others involved proves to be much more time consuming than with initial reporting by telephone. Even when detailed special forms are used, our own structured special

questionnaire included, the information needed depends so much on vaccine, age and type and severity of the event, that this can not be covered by one single form. Mandatory forms may delay reporting and may diminish reporting rate, since they are more time consuming for the reporter as well.

7.3 Underreporting

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

7.3.1 Reporters

Most notifications came from Child Health Clinic staff and the rise in number is near totally attributable to the clinics. But nearly half the children (375 +43 clinic) were seen by their GP or in hospital because of the event but only 70 were reported by them. We do not feel that this results in substantial loss of notifications because there is always the safety net of the clinic where is asked after adverse events specifically. Sometimes however the clinic staff assumes that the GP or paediatrician will have reported the event, or if not, it is apparently not important to do so. Especially events after MMR1 may be missed more often. The clinic visits after MMR are much more time spaced and the applicable interval after the vaccination is wider and much less precise. Reporting by hospital staff or GP is however of advantage because notifications are earlier received with more close signal detection and more accurate information without selective memory problems. Even if the adverse event will not be missed altogether, the reporting by GP or Hospital may save time because the event can be evaluated before the next clinic visit with unambiguous advice. One of the pitfalls is that the illness is inadvertently thought to be vaccine related and that there is an undue delay in diagnosis/recognition of an unrelated coincidental disease with (too) late treatment. On the other hand clearcut collapse reactions must not be treated as anaphylactic shock or as ALTE (Apparant Life Threatening Event or near-sids) with the whole diagnostic protocol worked through. GP's and also paediatricians need extra attention in educational activities on adverse events and contra-indications of the vaccination programme.

7.3.2 Geographical Distribution

The distribution of the reporting rates over the different regions is again more even than the year before, as in 1994.¹⁰ For all but three regions the confidence interval contains the countries average. Since these three regions have only 4-7000 new-borns a year this does not have much impact; applying the average of 4.2 per 1000 to these regions will only result in 15 reports more or, or less. In Den Haag there is a downward trend which is remarkable also because this is historically one of the most consistent reporting area's. It may well be chance but in order to check on reporting criteria a questionnaire is prepared. Overall the more even distribution is regarded as a sign of diminished underreporting.

Lowest rates are from area's where child Health Care is less professionalised and GP's have clinics for their own patients. Some regional variance of reporting rate is acceptable because "soft" criteria as need for consultation and advice and parental apprehension play a role in reporting. The wide reporting criteria are however a tool against underreporting and are helpful in detecting new and rare side effects.

7.3.3 Type of Events

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

For febrile convulsions a recent prospective study in the Netherlands disclosed 1 febrile convulsion after MMR (and none after DPTP), mounting up to approximately 1 in 10000 children.¹⁸ The 23 and 25 febrile convulsions following MMR and DPTP respectively seems to be compatible with this figure.

For collapse after DPTP vaccinations only two small prospective studies were done with incidence rates of 1:1750 and 1:2780.¹⁸⁻²⁰ 137 collapse reactions were reported in 1995. This amounts to about 1 in 1500 children. The relative frequencies are comparable to 1994 with the decrease in reported persistent screaming as exception.¹⁰ The increase in discoloured legs seems striking but must be interpreted with care, because in 1994 and before this was not considered a separate category, with application of case definitions. See under paragraph 7.8.2.

For Idiopathic Thrombocytopenic Purpura (ITP) following MMR there seems to be consistent underreporting. According to the literature ITP may follow MMR in up to 1 in 23000 children.^{21,22} Our reporting rate is 2-3 every year. Moreover most reports of ITP come in when the second MMR is due, some seven years later! Active surveillance with data linkage is planned as soon as PEA databases do include the exact vaccination date instead of month and year of vaccination. Hospital admission information on date and diagnosis must be accurate also however. ITP could also be included in the periodic sentinels among paediatricians, which may also reveal incidence rates of ITP in the Netherlands.

7.4 Age and Sex Distribution

The remarkable over representation of reports following the first vaccinations reflects several different factors. First the young age of the children with the inherent apprehension of the parents. It is often the first time the child is (made) sick. But also there are several frequent age specific adverse reactions as well as age specific chance occurrences. As part of good professional standards, clinic staff ask after adverse events before administering the next dose of vaccines. It is conceivable that there is also a certain degree of “getting used to” (common) reactions like fever, local inflammation and crying, with subsequent lower reporting rates as age progresses (higher dose numbers). DPTP is more reactogenic than MMR.

Like in previous years there is still some overrepresentation of boys in most categories, though a little less than in 1994. For collapse reaction and minor illness this is most consistent over the years.

The 4 to 1 rate of death, though not vaccine related, may reflect the greater frequency of infant deaths in boys. For most categories it is not possible to exclude selective reporting by sex, because of lack of background/incidence rates.

7.5 Diagnosis, Additional Information and Follow-up

Verification and additional information with follow up is considered important in the monitoring of the safety of the vaccination programme. Categorisation is done using the diagnostic criteria for case definitions. For the aggregated analysis all cases have been reappraised.

Discrepancy is often large between reported diagnosis and final diagnosis. This is partly due to different case definitions, but mostly because of more detailed information and more specific knowledge, skills and experience of the physicians of LVO. The value of a detailed account by the parents, especially in case of paroxysmal events, can not be overrated. Careful history talking after the first panic has subsided is of great importance. Especially collapse reactions are often reported as something else, like ALTE or near-sids, convulsion, anaphylactic shock, allergic reaction, encephalopathy etceteras. This is not as surprising as it may seem. A GP with an average of 30 new-borns a year may come across collapse reactions after vaccination only once in 50 years! And for

paediatricians also it is a rather rare entity. One tends to mild symptoms in known diagnostic categories. But on the other hand reported collapse reaction is not always collapse. Often there is only pallor or only apathy or just drowsiness or excessive sleep/difficulty in awakening.

Skin symptoms tend to cause great concern because of the feared anaphylactic reactions following the next dose. Like in former years most children with skin symptoms, even if apparent/occurring in close time relationship with the vaccination get a subsequent dose without recurrence. Severe anaphylactic reactions have not been known to happen with the vaccines of the RVP. We prefer descriptive terms for skin symptoms as well as for other categories, with no reference to possible pathophysiologic mechanisms, like allergic reaction for which there seems no justification most of the time.

The use of strict case definitions assures homogeneous diagnostic groups with possibility of epidemiological studies for risk factors and sequelae. Together with follow up this may lead to founded adjustment of indications, contra-indications, vaccines or schedules as well as to certain precautions when administering a next dose. For collapse reactions this kind of follow up study has shown a very low rate of recurrence after further pertussis vaccinations.²³ See also paragraph 7.8.1.

7.6 Causality Assessment

Assessing causal relation is regarded important in monitoring the safety of the vaccination programme. Not everything happening after vaccination is caused by the vaccination of course. Safety surveillance with causality assessment by RIVM and GR makes liberal reporting criteria possible and therefore more sensitive signal detecting. Careful causality assessment may free the programme from the burden of severe but unrelated adverse events as well as detect new rare adverse reactions. For causal relation five different categories are used, for the purpose of international comparison. International comparison is hampered however because of different criteria for surveillance systems, diagnostic procedures and causality assessment.

Only 1% of the reports did not allow causality assessment, mostly by lack of information about time interval or symptoms. All unclassifiable events were considered minor. Overall 81% of reports was considered adverse reaction, a little less than in 1994 (84%); this may reflect decreased underreporting. Comparison of RIVM with GR assessment shows a remarkable consistency.

7.7 Specific Events

About half of the reports concern mild or moderate local or systemic symptoms. Quite often notification was because of the need for consultation. Especially skin symptoms seemed to cause uncertainty. In the history of the RVP no severe/life threatening allergic reactions have been reported; children usually receive further vaccination in normal clinic setting. Experience for a number of years of uneventful MMR vaccination in children with chick eggwhite protein allergy, along with information of international studies, lead to adjustment of the procedures and the text of the package inserts.²³

The other half of the reported events were the so called major events, not severe per se, but more a historical annotation of certain dramatic events. Hospital admission is not major automatically. In this respect reporting criteria differ from assessment criteria. Some specific events are discussed below.

7.7.1 Collapse

This well known acknowledged adverse reaction is very frightening to parents. From 1993 onwards this reaction is no longer considered a contra-indication to further pertussis vaccinations.^{24,24,24,25}

Follow up has shown recurrence to be rare. In none of the 171 children (1994 and 1995 combined) with collapse reported after the first DTP/Hib vaccinations collapse recurred after subsequent vaccinations (c.i. 0-2.1%).²³ The pathophysiologic mechanism has not been made clear, nor have risk factors been defined. A patient-control study of collapse reactions reported in 1995 will be published separately. The total number of reported collapse reactions in 1994 and 1995 were more or less equal (134 and 137). As in 1994, strict case definitions have been applied. Three collapse reactions followed discoloured legs (see below)

7.7.2 Discoloured Legs

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

There is an increase in the number of reports. Although this phenomenon was reported in the years before the introduction of Hib in the programme, it seems to be much more frequent now. Association with the Hib vaccination remains speculative.

Discoloured legs were initially reported as, anaphylactic shock, Henoch Schonlein disease, sepsis, meningitis, allergic reaction, convulsion and severe local reaction, among others.

7.7.3 Meningitis

In this reporting year only four meningitis cases were diagnosed (the two children who died because of meningococcal septicaemia, excluded). All were considered coincidental and not related to the vaccination. Nor was there an undue delay in therapy because of the vaccination. A few children with discoloured legs with or without petechiae and fretfulness were hospitalised with suspected meningitis. As were some with signs of meningismus and irritability in whom no meningitis could be diagnosed. Data linkage studies are planned, also for the purpose of phase three clinical trial of anti meningitis vaccines.

As in other years a few children with bulging fontanel were reported, one grouped under major illness because of the body temperature, the other two under minor illness. Causal relation with the vaccine, even in case of consistent time interval, remains speculative.

7.7.4 Idiopathic Thrombocytopenic Purpura

Two cases with ITP were reported after MMR vaccination. One was considered a possible reaction to the vaccination. Because of the apparent underreporting a active surveillance study is under consideration.

7.7.5 Diabetes Mellitus

No cases of Diabetes Mellitus were reported. Cases reported in The periodic sentinel studies of Dutch paediatricians (NSCK) are checked retrospectively on the timing of Hib and MMR vaccinations (in collaboration with TNO&PG).^{26,27} Evaluation showed that the increase in the incidence rate of DM started well before the introduction of Hib vaccinations in the Netherlands, and did not coincide with the start of routine Hib vaccinations as in other countries (where Hib vaccinations were included years earlier than in the Netherlands). Reappraisal of earlier studies in Finland showed the increase in DM incidence rate not to be associated with Hib vaccinations. (pertussis, Sweden and MMR Sweden PM)²⁸⁻³¹

7.7.6 Death

Deaths were reported five times; none were considered caused or potentiated by the vaccinations. The vaccination did not cause confusion or delay in the diagnosis as is known to occur sometimes.

7.8 Prevention of Side Effects

Contra-indications are meant to prevent adverse reactions. They are the result of the balance of the risk of the target diseases, underlying disorders and the risk of vaccination.

Currently for DPTP no contra-indications are valid anymore. Individual adjustment of the schedule or precautions and special counselling of parents may be opted for, in special circumstances.

Of course good procedures of vaccine distribution and administration are of importance, including cold chain procurement and disinfecting the vials. Faulty procedures have not been implicated in any the reported adverse events this year again.

Excessive cooling of the injection site may increase local reactions, Fierce rubbing/massaging of the injection site straight after administration however may diminish local complaints and shorten crying because of distraction. Data are lacking of the effect on injection site symptoms of local/regional/individual procedures like application yoghurt, cabbage leaves, cucumber, menthol ointment and several homeopathic or herbal remedies. These procedures may have their own side effects!

Vaccinations under the RVP are routinely done in child health clinic setting. Emergency sets of corticoids, epinephrine and antihistaminics are not available in accordance to the guidelines of the Inspectorate of Health Care. These sets have never been necessary so far and availability may lead to inadvertent use. Routine paracetamol prophylactics is advised against but sometimes prophylactics seems reasonable after severe complaints following prior vaccinations or in preventing fever in children with a history of febrile convulsions. Paracetamol may be used in case of excessive crying or severe pain. But fever should be primarily be handled by cool clothing and cold sponging. It is most important that parents are advised to consult their GP in case of severe symptoms, so that concomitant disease will not be overlooked and (fatal) delay is avoided. However in case of clear-cut reactions like collapse or discoloured legs initial assessment suffices and one should not go through the whole ALTE protocol or allergic/neurological screening.

Attention should be paid not only to education of parents but also to education of GP's and paediatricians in this respect. Vaccine adverse reactions should be included in the differential diagnosis, nothing more but nothing less.

Deferral or discontinuation of vaccines or components because of adverse events should be considered an indirect side effect of vaccination and should be avoided. It should be stressed that serious adverse reactions are extremely rare and that lasting adverse effects do not occur. Vaccination in (outpatient) day care in hospital may alleviate parental anxieties in rare instances, it is however not a medical necessity.

7.9 Future Considerations

Consolidation of the current good reporting practices of clinic staff, with continuous education, also of GP's and paediatricians, is an aspect of a good performing of the vaccination programme. The low threshold 24h telephone service for reporting, consultation and advice is of great value for the current adverse event enhanced passive surveillance system. The quality of data generated by this system allows systematic follow up and study of specific adverse events. Subsequently adjustment of contra-indications and precautions may follow. Detailed trend analysis of specific adverse events, schedules and vaccines or lots will only be possible if a robust database system is available.

Active surveillance to check on overall tolerability, partly achieved in phase II and III trials in which the registered vaccines are used in the control groups, is planned in phase IV trials. For rare adverse events, like meningitis or ITP other strategies must be considered. Data linkage possibilities are being explored. A serious drawback is the lack of exact dates of vaccination in the PEA databases. Only four of the thirteen databases include lot numbers. Also the (adherence to the) case definitions in hospital admission or discharge or mortality registers should be secured.

International collaboration on adverse event surveillance and studies should be expanded.

A good quality safety monitoring system such as exists in the Netherlands cannot be taken for granted but requires maintenance and investment. New epidemiological designs and techniques may expand the knowledge on adverse events, an adequate database system is a prerequisite for this. But also the quality of data put in must be good of course. With the successful prevention of the target diseases the relative weight of adverse events increases. Parents and providers expect careful safety monitoring of the vaccinations. Anti vaccine movements will be more active in the future. A comprehensive surveillance system will be instrumental in combating unfounded allegations.

8. Conclusions and Recommendations

In 1995 the increase in reported adverse events continued though at a slower pace. This appears to reflect a further decline in underreporting. Febrile convulsions and collapse reactions seen to have a stable reporting rate, consistent with the incidence rate from prospective studies. The increase in reported discoloured leg phenomenon should be studied, with retrospective analysis of previous (pre Hib) years and reassessment according to the current case definitions

Detailed study of epidemiology, sequelae, follow up and risk factors should be performed regarding some specific adverse events.

The 24h telephone service for reporting, consultation and advice is an efficient and important tool of the enhanced passive safety surveillance system. Quality should be maintained.

The planned database system will allow further detailed aggregated analysis of the reports and will also facilitate systematic feed back to the reporters as well as data exchange with other bodies, national and international.

Active surveillance of adverse events, through sentinel study and data linkage is planned in addition to the passive surveillance. Possibilities for study of extremely rare severe events and long term effects is explored. Safety surveillance systems of the future should be prepared to be ready to study signals of specific rare or long term adverse effects on short notice. Especially now the introduction in the RVP of more (novel) vaccines is foreseen in the forthcoming years. This information may be necessary to counteract allegations of anti-vaccine movements. A problem is that one does not know what the next signal will be. International collaboration should be expanded, towards a comprehensive safety surveillance network of the childhood vaccination programmes. This may also be of help to perform the specific studies and increase scientific knowledge about adverse events following vaccinations. Eventually this will all boost public confidence in the programmes.

For the coming year is planned:

- implementation of a database system
- accelerated annual reports of 1996/1997
- annual report of 1998
- maintenance and evaluation of the current passive surveillance system
- report on descriptive epidemiology of collapse reactions
- report on patient-control study of collapse reaction
- report on descriptive epidemiology of discoloured legs
- exploration of possibilities of data linkage or sentinel studies
- active study of tolerability of DPTP/Hib vaccinations also in relation to the younger age schedule.

We plan to keep up a thorough high quality safety surveillance system and to stimulate reporting in the coming year. Only then it can be shown that the vaccination programme is safe. The total of 800 reports must be regarded in relation to a total of more than 2 million vaccines administered and of over 6 million components.

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Appendix 1 Mailing list

1	Hoofdinspecteur Preventieve en Curatieve Gezondheidszorg
2	Directeur-Generaal Volksgezondheid
3	Inspectie Gezondheidszorg, Inspecteur Infectieziekten
4	Gezondheidsraad, Den Haag voorzitter
5	Gezondheidsraad, Den Haag secretaris werkgroep RVP
6-22	Safety Surveillance Systems (diverse buitenlandse instellingen)
23	Depot Nederlandse Publikaties en Nederlandse Bibliografie
24	Directie RIVM
25	Directeur sector Vaccins
26	Directeur sector Volksgezondheidsonderzoek
27-29	Hoofd LVO
30-31	Hoofd LCB
32-33	Hoofd LPO
34-35	Hoofd LVR
36-37	Hoofd KRZ
38	Hoofd CIE
39	Hoofd LIS
40	Hoofd LIO
41	College ter Beoordeling van Geneesmiddelen
42	LAREB
43-60	Medisch Adviseurs Entadministraties
61	Landelijke Vereniging Entadministraties
62	Landelijk Coördinatiestructuur Infectieziektenbestrijding
63	Landelijk Coördinatiecentrum Reizigersadvisering
64-69	Auteurs
94	SBD/Voorlichting en Public Relations
95	Bureau Rapportenregistratie
96	Bibliotheek RIVM
97-107	Bureau Rapportenbeheer
108-140	Reserve

Appendix 2 Vaccination programme 1995

STAATSTOEZICHT
OP DE VOLKSGEZONDHEID



**Geneeskundige Hoofdinspecteur
van de Volksgezondheid**

VACCINATIEPROGRAMMA 1995

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

1995	1994	1991	1986
DKTP + Hib	DKTP + BMR	DTP	DTP + BMR

1. ZUIGELINGEN en KLEUTERS

VACCINATIESCHEMA

- DKTP (Difterie - Kinkhoest - Tetanus - Poliomyelitis)

Op de leeftijd van respectievelijk 3, 4 en 5 maanden wordt één DKTP- injectie gegeven. De vierde DKTP-injectie wordt tenminste zes maanden na de derde DKTP-injectie gegeven.
Dosering: 1 ml INTRAMUSCULAIR.

LET OP

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

Indien de kinkhoestvaccinatie gecontraïndiceerd is (zie Nederlands Tijdschrift voor Geneeskunde 1989; 133, nr. 40, blz. 1975-1977) en in plaats van DKTP, DTP wordt gegeven, dient degene die de enting verricht dit **duidelijk** te vermelden op de oproepkaart, die naar de entadministratie wordt gezonden.

- Hib (Haemophilus influenzae type b)

Op de leeftijd van respectievelijk 3, 4 en 5 maanden wordt één Hib- injectie gegeven. De vierde Hib-injectie wordt tenminste zes maanden na de derde Hib-injectie gegeven.
Alleen kinderen geboren vanaf 1 april 1993 komen in het kader van het vaccinatieprogramma voor deze vaccinatie in aanmerking.
Dosering: 0,5 ml INTRAMUSCULAIR.

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

Het verdient aanbeveling om een standaardprocedure aan te houden in welke ledematen de Hib- en DKTP- entingen worden toegediend, in verband met de herkenning van (mogelijke) bijwerkingen.

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

- BMR (Bof - Mazelen - Rodehond)

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

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

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

Het BMR-vaccin dient niet eerder dan op de leeftijd van veertien maanden te worden toegediend.

- DTP (Difterie - Tetanus - Poliomyelitis)

De in 1991 geboren kinderen worden in 1995 gerevaccineerd met DTP- vaccin. Afhankelijk van de reeds vroeger gegeven entingen worden 1, 2 of 3 injecties gegeven (zie Nederlands Tijdschrift voor Geneeskunde 1987; 131 nr. 15, blz. 641).
Dosering: 1 ml INTRAMUSCULAIR.

2. SCHOOLKINDEREN

VACCINATIESCHEMA

De in 1986 geboren kinderen worden in 1995 gerevaccineerd met DTP- vaccin. Afhankelijk van de reeds vroeger gegeven entingen worden 1, 2 of 3 injecties gegeven; zie ook onder 1.
Dosering: 1 ml INTRAMUSCULAIR.

De in 1986 geboren kinderen krijgen in 1995 een BMR-injectie.
Dosering: 0,5 ml SUBCUTAAN.

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

3. ENTADMINISTRATIES

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

PROVINCIE	ADRES	TELEFOON	FAX
GRONINGEN	Gorechtkade 8, 9713 CA Groningen	050-686350	050-138404
FRIESLAND	Sixmastraat 2, 8932 PA Leeuwarden	058-890555	058-891144
DRENTHE	Lauwers 9, 9405 BL Assen	05920-95260	05920-54224
OVERIJSSSEL	Strangeweg 25, 7731 GV Ommen	05291-55717	05291-55805
FLEVOLAND	Strangeweg 25, 7731 GV Ommen	05291-55717	05291-55805
GELDERLAND	Korte Coehoornstraat 2, 6811 LB Arnhem	085-429242	085-434999
UTRECHT	Zoutkamperschans 7, 3432 TZ Nieuwegein	03402-81376	03402-81517
NRD-HOLLAND	Zeilmakerstraat 40, 1991 JC Velsbroek	023-382454	023-386822
AMSTERDAM	Nieuwe Achtergracht 100, 1018 WT Amsterdam	020-5555460	020-5555360
ZD-HOLLAND	Europaweg 141, 2711 EP Zoetermeer	079-418238	079-315047
ROTTERDAM	Schiedamsedijk 95, 3011 EN Rotterdam	010-4339517	010-4339237
ZEELAND	Magnolia 55, 4461 EV Goes	01100-49246	01100-49240
NRD-BRABANT	Boscheweg 57, 5056 KA Berkel-Enschot	013-384849	013-384848
LIMBURG	Kleine Steeg 7, 6131 KJ Sittard	046-596262	046-529733

4. ALGEMEEN

4.1 ORGANISATIE.

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

4.2 VACCINDISTRIBUTIE.

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

4.3 REGISTRATIE EN VERANTWOORDING.

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

4.4 FINANCIERING.

De kosten van de uitvoering van het vaccinatieprogramma komen ten laste van de in de A.W.B.Z. geregelde verzekering. Per verrichte enting wordt een bedrag uitbetaald aan de Provinciale Entadministraties. De Provinciale Entadministraties zullen volgens landelijke richtlijnen zorgdragen voor doorbetaling van de ter beschikking gestelde gelden aan de meewerkenden aan het vaccinatieprogramma.

4.5 Kinderen tot 13 jaar die niet of niet volledig zijn ingeënt volgens het voor die jaarklasse geldende entschema, kunnen de nog **noodzakelijke** entingen kosteloos ontvangen in het kader van het vaccinatieprogramma.

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

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

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

- 4.7 Alle nadere regelingen welke met betrekking tot het vaccinatieprogramma 1995 worden getroffen, vereisen de goedkeuring van de Geneeskundige Hoofdinspecteur van de Volksgezondheid en de Regionale Geneeskundige Inspecteurs van de Volksgezondheid.
- 4.8 Exemplaren van deze folder kunnen worden aangevraagd bij de Geneeskundige Hoofdinspecteur van de Volksgezondheid, Sir Winston Churchilllaan 362, postbus 5406, 2280 HK Rijswijk, telefoon 070-3405486.
- 4.9 Voor vaccinaties, gegeven overeenkomstig bovengenoemd vaccinatieprogramma, doch zonder tussenkomst van de Provinciale Entadministraties, wordt GEEN gratis vaccin ter beschikking gesteld, noch enige vergoeding gegeven.

5. BIJWERKINGEN

Na vaccinaties kunnen in zeldzame gevallen ernstige bijwerkingen optreden.

Elke bijwerking kan de vaccinatiegraad negatief beïnvloeden.

Melding van (mogelijke) bijwerkingen aan het Rijksinstituut voor Volksgezondheid en Milieuhygiëne (RIVM) te Bilthoven, onder vermelding van het partijnummer van het betreffende vaccin is dan ook dringend gewenst (tel. 030-742424).

6. VACCINATIESCHEMA PER KIND

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

Rijswijk, december 1994

De Geneeskundige Hoofdinspecteur
van de Volksgezondheid,

G.H.A. Siemons, arts.

Appendix 3 Instruction leaflets DKTP



RIJKSINSTITUUT
VOOR VOLKSGEZONDHEID
EN MILIEU

DIFTERIE-, KINKHOEST-, TETANUS-, POLIOMYELITISVACCIN

40002

Beschrijving en samenstelling

DKTP vaccin is een gecombineerd vaccin tegen difterie, kinkhoest, tetanus en poliomyelitis. Difterie- en tetanustoxoïde zijn bereid uit toxines geproduceerd door respectievelijk *Corynebacterium diphtheriae*, stam Parke Williams nr. 8 en *Clostridium tetani*, stam Harvard 49205. De kinkhoest component is een suspensie van hitte geïnactiveerde *Bordetella pertussis* bacteriën, stammen 134 en 509. De poliomyelitiscomponent bestaat uit geïnactiveerd en gezuiverd virus van de 3 typen: type 1 stam Mahoney, type 2 stam MEF 1 en type 3 stam Saukett. Aan het gecombineerde vaccin zijn als conserveermiddelen 2-fenoxyethanol en formaldehyde toegevoegd.

1 dosis (1 ml) bevat:		
difterietoxoïde	≥ 30	IE *
kinkhoestvaccin	4	IE
tetanustoxoïde	≥ 60	IE
geïnactiveerd poliovirus:		
type 1	40	DE **
type 2	4	DE
type 3	7,5	DE
aluminiumfosfaat	1,5	mg
2-fenoxyethanol	5	mg
formaldehyde	0,025	mg

*) IE = Internationale Eenheid

**) DE = D-antigeneenheden (eenheid voor poliomyelitiscomponent)

Farmaceutische vorm en presentatie

DKTP vaccin is een suspensie voor injectie en wordt afgeleverd in:
flesjes à 1 ml (1 dosis) bestelnr. 360.1

Fabrikant en registratiehouder

RIVM, Postbus 1, 3720 BA Bilthoven
afd. verkoop SVM
Postbus 457, 3720 AL Bilthoven
Tel.: 030-748010
Vanaf 10 oktober 1995: 030-2748010

RVG nummer

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

Indicatie

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

Contra-indicaties

- bekende overgevoeligheid voor bestanddelen van dit vaccin.
- ernstige reactie na eerdere toediening van hetzelfde vaccin.

Bij DKTP vaccin vormen de volgende reacties na eerdere toediening een contra-indicatie: convulsie, collaps en encephalopathie.

Ten aanzien van de kinkhoestcomponent geldt dat kinderen die een convulsie hebben doorgemaakt of lijden aan progressieve neurologische aandoeningen, niet met DKTP vaccin worden geënt. In dat geval kan DTP vaccin worden gegeven volgens het DKTP schema.

Speciale waarschuwingen en voorzorgen bij gebruik

Na enige tijd staan, ontstaat een bezinskel. 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 gezwinkt worden tot een homogene suspensie is verkregen.

De kleur van het vaccin wordt veroorzaakt door de kleurstof fenolrood (pH-indicator) en mag variëren van oranjegeel tot oranje-rood. Indien de kleur duidelijk geel of violet is, mag het product niet worden gebruikt. De kleurindicator zegt niets over overschrijding van de bewaar temperatuur.

Dosering en de wijze van gebruik

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

Ongewenste bijwerkingen

Na toediening van DKTP vaccin kunnen lokale reacties optreden, die soms gepaard gaan met verschijnselen van algemene malaise en koorts. In zeldzame gevallen kan de kinkhoestcomponent in het vaccin aanleiding geven tot een ernstige reactie zoals collaps of convulsie. Ook treedt sporadisch een toestand van encephalopathie na DKTP vaccinatie op. Dergelijke complicaties worden waargenomen in een periode van 1 uur tot 3 dagen na enting. De meeste ernstige reacties worden binnen 12 uur gezien.

Artsen en apothekers wordt verzocht mogelijke bijwerkingen en in het bijzonder die bijwerkingen die niet in deze bijsluiter zijn genoemd, te melden aan de afdeling Klinisch Onderzoek van het Laboratorium voor Veldonderzoek Vaccins van het RIVM, tel. 030-742424. Vanaf 10 oktober 1995: 030-2742424.


Bewaring

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


Uiterste gebruiksdatum

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

Juni 1995

RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEUHYGIENE — BILTHOVEN		Toepassing Immunisatie van zuigelingen en peuters.	
		Entschema 4 x 1 ml intramusculair. De eerste drie doses worden gegeven met steeds één maand tussentijd, bij voorkeur op de leeftijd van respectievelijk 3, 4 en 5 maanden, echter niet eerder; de vierde dosis wordt tenminste 6 maanden na de derde enting toegediend, dus op zijn vroegst op de leeftijd van 11 maanden. De vierde dosis mag ook in dezelfde zitting als de BMR vaccinatie worden gegeven, dus op de leeftijd van 14 maanden.	
DIFTERIE-, KINKHOEST-, TETANUS-		Revaccinatie Revaccinatie geschiedt met DTP-vaccin, dus een vaccin zonder kinkhoestcomponent.	
POLIOMYELITISVACCIN		Contra-indicaties In zeldzame gevallen kan de kinkhoestcomponent in het vaccin aanleiding geven tot ernstige reacties als shock of een reactie van het centrale zenuwstelsel. Deze laatste varieert van een kortdurende convulsie tot een ernstige encephalopathie. Dergelijke complicaties worden waargenomen in een periode van één uur tot 3 dagen na de DKTP-enting, met dien verstande dat de meeste reacties binnen 12 uur na enting worden gezien. DKTP-vaccinatie is gecontraïndiceerd bij kinderen die een convulsie hebben doorgemaakt. Ook het optreden van een complicatie vormt een contra-indicatie voor een volgende enting met DKTP-vaccin. In deze gevallen wordt met DTP-vaccin gevaccineerd, echter volgens het DKTP-entschema. Indien na DKTP-vaccinatie één van de bovengenoemde complicaties optreedt, is melding hiervan aan het RIVM dringend gewenst (tel. 030 - 74 25 95 medisch centrum voor vaccinzaken).	
Gecombineerd, geadsorbeerd vaccin tegen difterie, kinkhoest, tetanus en poliomyelitis			
Samenstelling 1 dosis (1 ml) bevat:			
difterietoxoïde	15	Lf	
kinkhoestvaccin	16	IOE	
tetanustoxoïde	5	Lf	
geïnactiveerd gezuiverd poliomyelitisvaccin			
type 1	tenminste	20	DE
type 2	tenminste	2	DE
type 3	tenminste	3,5	DE
aluminiumfosfaat		1,5	mg
2-fenoxyethanol		5	mg
formaldehyde		25	µg
De kleur van het vaccin wordt veroorzaakt door fenolrood en mag variëren van oranjegeel tot oranje-rood. Indien de kleur duidelijk geel of violet is, mag het produkt niet worden gebruikt. Het vaccin bevat geen antibiotica.			
Vóór gebruik goed schudden.			
Bewaring Bij 2—8 °C; voorkom bevroering.			
Houdbaarheid De houdbaarheidstermijn staat op elke verpakking aangegeven. Het produkt dient na die datum niet meer te worden gebruikt.			
Dosis per enting 1 ml intramusculair.			
3000 / 1		Verpakking ampul à 1 ml flesje à 10 ml	
		Bestelnr. 360.1 Bestelnr. 360.10	
RIVM, Postbus 1, 3720 BA Bilthoven, Tel. 030 - 749111			
3000/1			

Appendix 4 Instruction leaflet DTP

 <p>RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEU</p> <p>BILTHOVEN - NEDERLAND</p> <p>DIFTERIE-, TETANUS-, POLIOMYELITISVACCIN</p> <p>4001/1</p>	<p>Fabrikant en registratiehouder RIVM, Postbus 1, 3720 BA Bilthoven afd. verkoop SVM Postbus 457, 3720 AL Bilthoven Tel.: 030-748010 Vanaf 10 oktober 1995: 030-2748010</p> <p>RVG nummer DTP vaccin is in het register ingeschreven onder RVG-nummer 17641.</p>																											
<p>Beschrijving en samenstelling</p> <p>DTP vaccin is een gecombineerd vaccin tegen difterie, tetanus en poliomyelitis. Difterie- en tetanustoxoïde zijn bereid uit toxines geproduceerd door respectievelijk <i>Corynebacterium diphtheriae</i>, stam Parke Williams nr. 8 en <i>Clostridium tetani</i>, stam Harvard 49205. De poliomyelitiscomponent bestaat uit geïnactiveerd en gezuiverd virus van de 3 typen: type 1 stam Mahoney, type 2 stam MEF I en type 3 stam Saukett. Aan het gecombineerde vaccin zijn als conserveermiddelen 2-fenoxyethanol en formaldehyde toegevoegd.</p> <p>1 dosis (1 ml) bevat:</p> <table border="0"> <tr> <td>difterietoxoïde</td> <td>≥ 5</td> <td>IE *</td> </tr> <tr> <td>tetanustoxoïde</td> <td>≥ 20</td> <td>IE</td> </tr> <tr> <td>geïnactiveerd poliovirus:</td> <td></td> <td></td> </tr> <tr> <td>type 1</td> <td>40</td> <td>DE **</td> </tr> <tr> <td>type 2</td> <td>4</td> <td>DE</td> </tr> <tr> <td>type 3</td> <td>7,5</td> <td>DE</td> </tr> <tr> <td>aluminiumfosfaat</td> <td>1,5</td> <td>mg</td> </tr> <tr> <td>2-fenoxyethanol</td> <td>5</td> <td>mg</td> </tr> <tr> <td>formaldehyde</td> <td>0,025</td> <td>mg</td> </tr> </table>	difterietoxoïde	≥ 5	IE *	tetanustoxoïde	≥ 20	IE	geïnactiveerd poliovirus:			type 1	40	DE **	type 2	4	DE	type 3	7,5	DE	aluminiumfosfaat	1,5	mg	2-fenoxyethanol	5	mg	formaldehyde	0,025	mg	<p>Indicatie Actieve immunisatie tegen difterie, tetanus en poliomyelitis. DTP vaccin kan zowel voor primaire immunisatie (van volwassenen) als voor revaccinatie worden gebruikt.</p> <p>Contra-indicaties De algemene contra-indicaties die voor ieder vaccin gelden: - bekende overgevoeligheid voor bestanddelen van dit vaccin. - ernstige reactie na eerdere toediening van hetzelfde vaccin.</p> <p>Speciale waarschuwingen en voorzorgen bij gebruik Na enige tijd staan, ontstaat een bezinskel. Dit is een normaal verschijnsel en is niet van invloed op de kwaliteit van het vaccin. Alvorens het vaccin te gebruiken, moet het flesje enkele malen gezwenkt worden tot een homogene suspensie is verkregen. De kleur van het vaccin wordt veroorzaakt door de kleurstof fenolrood (pH-indicator) en mag variëren van oranjegeel tot oranje-rood. Indien de kleur duidelijk geel of violet is, mag dit vaccin niet worden gebruikt. De kleurindicator zegt niets over overschrijding van de bewaar temperatuur.</p>
difterietoxoïde	≥ 5	IE *																										
tetanustoxoïde	≥ 20	IE																										
geïnactiveerd poliovirus:																												
type 1	40	DE **																										
type 2	4	DE																										
type 3	7,5	DE																										
aluminiumfosfaat	1,5	mg																										
2-fenoxyethanol	5	mg																										
formaldehyde	0,025	mg																										
<p>*) IE = Internationale Eenheid **) DE = D-antigeen-eenheden (eenheid voor polio-componenten)</p> <p>Farmaceutische vorm en presentatie DTP vaccin is een suspensie voor injectie en wordt afgeleverd in: flesjes à 1 ml bestelnr. 340.1 flesjes à 10 ml bestelnr. 340.10</p>																												

Dosering en wijze van gebruik

Eén dosis DTP vaccin is 1 ml en dient intramusculair te worden gegeven.

Een basisimmunisatie voor reizigers wordt gegeven door een primaire serie van twee doses, met tenminste 1 maand tussentijd, gevolgd door een derde dosis, tenminste 6 maanden na de tweede dosis. De eerste toediening kan het best 4 tot 5 weken voor vertrek plaatsvinden, gevolgd door een tweede kort voor vertrek. Een volledige vaccinatie (3 x DTP) geeft 15 jaar bescherming.

Wanneer de laatste D(K)TP vaccinatie langer dan 15 jaar geleden heeft plaatsgevonden, dient de betrokkene als ongevaccineerd beschouwd te worden.

Kinderen die een volledige basisimmunisatie met DKTP vaccin (4 doses) hebben ontvangen, worden met DTP vaccin gerevaccineerd op de leeftijd van ca. 4 en ca. 9 jaar. Dit schema wordt in het Rijksvaccinatieprogramma (RVP) toegepast.

Volgens het RVP worden DTP en BMR vaccin op ca. 9 jarige leeftijd gegeven. Dit kan simultaan tijdens één entsessie, echter op verschillende injectieplaatsen. Als hiervan geen gebruik wordt gemaakt, dient een tussentijd te worden aangehouden van tenminste 2 weken indien DTP vaccin *vóór* de BMR vaccinatie is gegeven en van 4 weken indien DTP vaccin *na* de BMR vaccinatie wordt gegeven.

Ongewenste bijwerkingen

Lokale reacties kunnen voorkomen. Algemene reacties als malaise en koorts zijn weinig frequent.

Artsen en apothekers wordt verzocht mogelijke bijwerkingen te melden aan de afdeling Klinisch Onderzoek van het Laboratorium voor Veldonderzoek Vaccins van het RIVM, tel. 030-742424. Vanaf 10 oktober 1995: 030-2742424.

Bewaring

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


Multidoses flesjes zijn bedoeld voor groepstoepassing en moeten binnen 8 uur worden opgebruikt en gedurende die tijd in de koelkast worden bewaard.

Uiterste gebruiksdatum

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

Mei 1995

Appendix 5 Instruction leaflet Hib



**RIJKSINSTITUUT
VOOR VOLKSGEZONDHEID
EN MILIEU**

BILTHOVEN - NEDERLAND

40263

HAEMOPHILUS b CONJUGAAT (PRP-T) VACCIN

Haemophilus influenzae type b conjugaat vaccin
gevriesdroogd

Geproduceerd door Pasteur Mérieux sv - Lyon - France

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

Het gevriesdroogde vaccin bevat:

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

Het vaccin bevat geen adjuvantia of conserveermiddelen.

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

bestelnr. 380

Fabrikant
Pasteur Mérieux sérums et vaccins

Registratiehouder
RIVM, Postbus 1, 3720 BA Bilthoven
afd. verkoop SVM
Postbus 457, 3720 AL Bilthoven
Tel.: 030-748010
Vanaf 10 oktober 1995: 030-2748010

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

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

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

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

Dosering en de wijze van gebruik
Gebruik voor resuspenzie uitsluitend de bijgeleverde reconstitutievloeistof.
Resuspenzie geschiedt door 0,6 ml van de reconstitutievloeistof met een steriele spuit bij het gedroogde vaccin te voegen. Door het produkt voorzichtig om te zwenken ontstaat een heldere, kleurloze oplossing.
Eén dosis bestaat uit 0,5 ml vaccin, ongeacht de leeftijd. Het vaccin dient intramusculair te worden toegediend. Niet intraveneus spuiten.

Vaccinatieschema:
Het toe te passen vaccinatieschema is afhankelijk van de leeftijd bij het begin van de immunisatie. Daar zeer jonge kinderen de meest bedreigde groep vormen, dient zo vroeg mogelijk (bij voorkeur vanaf 3 maanden) met de immunisatie aangevangen te worden.

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

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

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

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

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

Juni 1995

Appendix 6 Instruction leaflet BMR

 <p>RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEU</p> <p>BILTHOVEN - NEDERLAND</p>	<p>RVG nummer BMR vaccin is in het register ingeschreven onder RVG-nummer 17654.</p> <p>Indicatie Actieve immunisatie tegen bof, mazelen en rubella vanaf de leeftijd van 14 maanden.</p> <p>Contra-indicaties - BMR vaccin bevat levende verzwakte virusstammen en toepassing is dan ook gecontraïndiceerd bij patiënten die met corticosteroiden of cytostatica worden behandeld en bij patiënten met stoornissen in het afweermecanisme, met uitzondering van HIV-infecties. - BMR vaccin is eveneens gecontraïndiceerd bij zwangerschap.</p> <p>Speciale waarschuwingen en voorzorgen bij gebruik - Bof- en mazelenvirus worden gekweekt in cellen afkomstig van kippe-embryo's. Overgevoeligheid voor kippe-eiwit is geen contraïndicatie; bij patiënten met anafylactoïde reacties op kippe-eiwit dient BMR vaccinatie echter onder strikte medische begeleiding te worden uitgevoerd. - Voor gelijktijdig toedienen van vaccins zie onder dosering en de wijze van gebruik. - Contraceptieve maatregelen moeten worden genomen tot 3 maanden na vaccinatie van vruchtbare vrouwen. - Aanbevolen wordt vaccinatie tegen BMR minstens 3 maanden uit te stellen na transfusie met totaal bloed of plasma en na toediening van immunoglobuline afkomstig van de mens.</p>
<p>BOF-, MAZELEN-, RUBELLAVACCIN</p> <p>levend, gevriesdroogd</p> <p>Licentie van Merck & Co., Inc. Rahway, N.J., U.S.A.</p>	<p>4002/3</p>
<p>Beschrijving en samenstelling</p> <p>Bof-, mazelen-, rubellavaccin (BMR) is een gevriesdroogd preparaat van levend verzwakt bofvirus, gekweekt op kippe-embryofibroblasten, stam Jeryl Lynn; levend verzwakt mazelenvirus, gekweekt op kippe-embryofibroblasten, stam Moraten, verkregen door de reeds verzwakte Edmonston stam door herhaalde passage in celculturen verder te verzwakken, en levend verzwakt rubellavirus, stam Wistar RA27/3, gekweekt op menselijke diploïde celculturen (WI-38).</p> <p>1 dosis (0,5 ml) bevat na resusensie met de bijgepakte reconstitutievloeistof:</p> <p>bofvirus ≥ 5000 p.f.u.*</p> <p>mazelenvirus ≥ 1000 p.f.u.</p> <p>rubellavirus ≥ 1000 p.f.u.</p> <p>Sorbitol en gehydrolyseerde gelatine zijn als stabilisatoren aan het vaccin toegevoegd.</p> <p>Het vaccin bevat geen antibiotica en geen conserveermiddel.</p> <p>*) p.f.u. = plaque forming unit</p>	
<p>Farmaceutische vorm en presentatie</p> <p>BMR vaccin is een poeder voor injectievloeistof en wordt afgevuld in: flesjes à 1 dosis, met even zoveel flesjes reconstitutievloeistof bestelnr. 442</p>	
<p>Fabrikant en registratiehouder</p> <p>RIVM, Postbus 1, 3720 BA Bilthoven</p> <p>afd. verkoop SVM</p> <p>Postbus 457, 3720 AL Bilthoven</p> <p>Tel.: 030-748010</p> <p>Vanaf 10 oktober 1995: 030-2748010</p>	

Dosering en de wijze van gebruik

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

Het Rijksvaccinatieprogramma voorziet in vaccinatie op een leeftijd van 14 maanden en een tweede vaccinatie op circa 9-jarige leeftijd.

De vaccinaties kunnen in dezelfde zitting gegeven worden met andere vaccins die in het Rijksvaccinatieprogramma worden toegepast, uiteraard op een andere injectieplaats.

Als hiervan geen gebruik wordt gemaakt, dient een tussentijd te worden aangehouden van tenminste 2 weken indien het D(K)TP en/of Hib vaccin *voor* de BMR vaccinatie is gegeven, en van 4 weken indien het D(K)TP en/of Hib vaccin *na* de BMR vaccinatie wordt gegeven.

Ook volwassenen kunnen met BMR vaccin worden geïmmuniseerd.

Ongewenste bijwerkingen

Vaccinatie kan gedurende korte tijd een branderig, stekend gevoel geven op de plaats van enting.

Koorts en/of erytheem kan optreden 5 tot 12 dagen na vaccinatie. Kinderen die met hoge temperatuur op vaccinatie reageren, kunnen, indien hiertoe gepredisponeerd, een febrile convulsie krijgen.

In zeer zeldzame gevallen zijn na vaccinatie encefalitis en andere reacties van het centraal zenuwstelsel waargenomen. Een oorzakelijk verband met vaccinatie kon daarbij niet worden uitgesloten; echter een verhoging van het aantal gevallen in vergelijking met niet-gevaccineerden is niet waargenomen. De rubella-component van het vaccin geeft bij kinderen weinig reacties. Soms wordt een zwelling van de cervicale of occipitale lymfeklieren waargenomen. Echter, vooral bij volwassen vrouwen, zijn 2 à 4 weken na vaccinatie passagère arthralgieën en arthritiden gezien. Sporadisch treden allergische reacties op.

Artsen wordt verzocht mogelijke bijwerkingen te melden aan de afdeling Klinisch Onderzoek van het Laboratorium voor Veldonderzoek Vaccins van het RIVM, tel. 030-742424. Vanaf 10 oktober 1995: 030 - 2742424.

Bewaring

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

Resterend vaccin dient te worden vernietigd b.v. door koken in water gedurende 10 minuten.

Uiterste gebruiksdatum

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

Mei 1995