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**Adverse Events Following Immunisation
under the National Vaccination
Programme of The Netherlands**
Number VIII - Reports in 2001

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Abstract

Adverse events following immunisation (AEFI) in the National Vaccination Programme of the Netherlands (RVP) have been monitored through an enhanced passive surveillance system by RIVM since 1962. From 1984 onwards evaluation is done in close collaboration with the Health Council. Reports are received mainly from Child Health Care professionals primarily 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 annual report on 2001 an overview of all reported AEFI is presented with classification according to case definitions and causality. Trend analysis, reporting bias, background rates of specific events and possible pathophysiology of symptoms are discussed. On a total of nearly 2.5 million vaccinations 1331 AEFI were reported. Of these 17 (1.3%) were unclassifiable because of missing information. In 82% (1091) of the classifiable events a possible causal relation with vaccination was established and in 18% (223) the events were judged to be coincidental. The increase in the number of notifications in 2001 (17% more than in 2000) is discussed.

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Abbreviations

AE	Adverse Event
AEFI	Adverse Event Following Immunisation (melding or postvaccinale gebeurtenis)
aK	Acellulair pertussis vaccine
AMK	Advice center and social services for child abuse and neglect
AR	Adverse Reaction (bijwerking)
BCG	Bacille Calmette Guérin (vaccine)
BHS	Breath Holding Spell
BMR	Bof Mazelen Rodehond vaccin (MMR)
CB	Child Health Clinic (consultatiebureau)
CBS	Statistics Netherlands
CIE	Centre for Infectious diseases Epidemiology (of RIVM)
DM	Diabetes Mellitis
DKTP	Difterie Kinkhoest Tetanus Polio vaccin (DPTP)
DTP	Diphtheria, Tetanus, (inactivated) Polio (vaccine)
DPTP	Diphtheria, Tetanus, (whole cell) Pertussis, (inactivated) Polio (vaccine)
EPI	Expanded Programme on Immunisation
GGD	Municipal Public Health Department
GP	General Practitioner, Family physician (huisarts)
GR	Health Council (Gezondheidsraad)
HepB	Hepatitis B (vaccine)
HBIG	Hepatitis B Immunoglobulin
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HHE	Hypotonic Hyporesponsive Episode (collapse)
Hib	Haemophilus influenzae type b (vaccine)
IGZ	Inspectorate of Health Care
IPV	Inactivated Polio Vaccine
ITP	Idiopathic Thrombocytopaenic Purpura
JGZ	Child Health Care (jeugdgezondheidszorg)
LAREB	Netherlands Pharmacovigilance Foundation
LTR	Laboratory for Vaccine Preventable Diseases (of RIVM)
MAE	Medical Consultant of PEA
MenC	Meningococcal C infection (vaccine)
MMR	Measles Mumps Rubella vaccine
NSCK	Netherlands Paediatrics Surveillance Unit
NVI	Netherlands Vaccine Institute
PEA	Provincial Immunisation Administration
PMS	Post Marketing Surveillance
PRP-T	Polyribosil Ribitol Phosphate Tetanus conjugate vaccine
RIVM	National Institute for Public Health and the Environment
RVP	Netherlands Vaccination Programme
SVM	Foundation for the Advancement of Public Health and Environmental Protection
TBC	Tuberculosis
WHO	World Health Organisation

Contents

Samenvatting 9

Summary 11

1 Introduction 13

2 Post Marketing Surveillance 15

3 The Netherlands Vaccination Programme 17

3.1 Vaccines and Schedule 17

3.2 Vaccine Distribution and Registration 18

3.3 Child Health Care System 18

3.4 Safety Surveillance 19

4 Materials 21

4.1 Post Vaccination Events 21

4.2 Notifications 21

5 Methods 23

5.1 Analysis 23

5.2 Additional Information 23

5.3 Working Diagnosis 23

5.4 Causality Assessment 23

5.5 Event Categories 25

5.6 Recording, Filing and Feedback 27

5.7 Health Council 28

5.8 Annual Reports and Aggregated Analysis 28

5.9 Quality Assurance 29

6 Results 31

6.1 Number of Reports 31

6.2 Reporters 32

6.3 Regional Distribution 33

6.4 Vaccines 36

6.5 Feedback to Reporters 39

6.6 Source of Information and Medical Intervention 40

6.7 Sex Distribution 41

6.8 Causal Relation 43

6.9 Categories of Adverse Events 44

- 6.9.1 Local reactions 44
- 6.9.2 Systemic symptoms 45
- 6.9.3 Persistent Screaming 49
- 6.9.4 General skin manifestations/phenomenon 50
- 6.9.5 Discoloured legs 51
- 6.9.6 Faints 52
- 6.9.7 Fits 53
- 6.9.8 Encephalopathy/encephalitis 54
- 6.9.9 Anaphylactic shock 54
- 6.9.10 Death 54

7 Discussion 57

7.1 Safety Surveillance of the RVP 57

- 7.1.1 Information Service, Reporting Route and Feedback 58
- 7.1.2 Verification and Assessment 59
- 7.1.3 Reporters 60
- 7.1.4 Source of Information 61
- 7.1.5 Regional Distribution and Reporting Rates 61
- 7.1.6 Passive Surveillance versus Active surveillance 61

7.2 Increase in Number of Reports 62

- 7.2.1 Underreporting 63
- 7.2.2 Distribution over Vaccines and Dose 63
- 7.2.3 Distribution over Events 63
- 7.2.4 Severity, Reporting Interval, Causality and Level of Intervention 64
- 7.2.5 Accelerated Schedule 65

7.3 Specific Events 65

- 7.3.1 Collapse reaction 65
- 7.3.2 Discoloured legs 66
- 7.3.3 Apnoea 66
- 7.3.4 Convulsions and Atypical Attacks 66
- 7.3.5 Local Reactions and Abscess 67
- 7.3.6 Skin Symptoms and Allergy 67
- 7.3.7 ITP, Gait disturbance (ataxia) 67
- 7.3.8 Anaphylactic shock 67
- 7.3.9 Encephalopathy 68
- 7.3.10 Pervasive Disorders and Retardation 68
- 7.3.11 Epilepsy 68
- 7.3.12 Death 69

7.4 Management of Adverse Events 69

- 7.4.1 Prevention and Treatment Adverse Events 70
- 7.4.2 Contraindications 70
- 7.4.3 Risk Communication 70
- 7.4.4 Causality Assessment 71

7.5 Considerations for the Safety Surveillance of the RVP 72

8 Conclusions and Recommendations 75

References 77

Appendix 1 Vaccination Programme of 2001 83

Appendix 2 Package insert DPTP 85

Appendix 3 Package insert DTP 87

Appendix 4 Package insert Hib 89

Appendix 5 Package insert MMR 91

Appendix 6 Package insert aK 94

Samenvatting

Vermoede bijwerkingen van vaccinaties van het Rijksvaccinatieprogramma (RVP) worden in Nederland centraal geregistreerd en beoordeeld door het RIVM sinds 1962. De bewaking van de veiligheid van het RVP gebeurt vanaf 1984 in nauwe samenwerking met de Gezondheidsraad (GR). De telefonische informatiedienst van het RIVM is een belangrijk instrument in dit passieve bewakingssysteem. 96% van de spontane meldingen komt telefonisch binnen, in hoofdzaak vanuit de Jeugdgezondheidszorg (90%). Nadere gegevens van anderen dan de melder, bijvoorbeeld van ouders, huisarts of ziekenhuis worden in circa 78% van de meldingen verkregen. Na aanvulling en verificatie volgt het stellen van een (werk)diagnose en causaliteitbeoordeling door artsen van het RIVM. De beoordeling wordt meestal (91%) 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 door hen geselecteerde meldingen individueel en de geaggregeerde gegevens van het jaarrapport steekproefsgewijs tijdens een jaarlijks werkbezoek aan het RIVM. De GR adviseert de Minister van Volksgezondheid jaarlijks over de veiligheid van het RVP. Dit advies wordt gebaseerd op het rapport van het RIVM en op wetenschappelijke studies over vaccins, die nu onderdeel zijn van het RVP of dat in de toekomst kunnen worden. Het RIVM jaarrapport bevat alle binnengekomen meldingen in een kalenderjaar.

Dit is het achtste jaarrapport.

In 2001 zijn 1331 meldingen binnengekomen, betreffende 1251 kinderen, op een totaal van bijna 2,5 miljoen vaccinaties per jaar. 17 Meldingen (13%) waren niet te beoordelen wegens het ontbreken van informatie. 82% (1091) van de meldingen werd als bijwerking beoordeeld met een mogelijk, waarschijnlijk of zeker causaal verband. Een toevallige samenloop werd aangenomen in 18% (233) van de meldingen.

Van de milde, zogenaamde “minor”, algemene, huid- of lokale verschijnselen (584) werden 425 (74%) meldingen als mogelijke bijwerking uitgeboekt in 2001, met 13 gevallen niet te beoordelen.

Verkleurde benen (in 1995 voor het eerst afgesplitst van de huidverschijnselen) werden 175 keer gemeld, met in op vijf na alle gevallen een mogelijke causale relatie.

Andere zogenaamde “major” postvaccinale gebeurtenissen (gerubriceerd onder convulsies, collaps, “ziek major”, lokaal major, een enkel huidverschijnsel, persistent screaming, encefalopathie en de sterfgevallen) werden 747 keer gemeld en in 87% (656) beoordeeld als mogelijke bijwerking met 4 meldingen niet te beoordelen.

Collaps, waaronder ook atypische en onvolledige episodes, werd 268 maal vastgesteld, met in 12 gevallen geen oorzakelijk verband. Daarnaast enkele keren Breath-Holding-Spells (5) en flauwvallen (20) in oudere kinderen. In 2001 werden 56 convulsies gemeld, waarvan vijf afebril, die in 45 gevallen (80%) als mogelijke bijwerking werden beoordeeld (met een melding niet te beoordelen). De 55 atypische aanvallen hadden in 78% (43) een mogelijk causaal verband. Epilepsie (10) werd in alle gevallen niet als bijwerking beoordeeld, maar als een coïncidentie. Persistent screaming (49) werd in alle gevallen gezien als bijwerking.

Koorts van $\geq 40,5^{\circ}\text{C}$ (met bij twee kinderen vooral langdurig koorts) was de werkdiagnose bij 38 kinderen uit de “ziek major” groep, op vijf na allemaal beschouwd als bijwerking. Van de 36 andere beelden uit de “ziek major” groep was er 10 keer een mogelijk causaal verband, geprikkeld gedrag (1), vaccinitis (4), in drie gevallen met ook zeer hoge koorts ($\geq 40,5^{\circ}\text{C}$). Daarnaast was er in de “ziek major” groep nog ITP (2), anemie (1), artritis (1) en ontregeling van een stofwisselingsziekte (1). De overige 26 meldingen waren coïncidenteel. Er waren 13 abcessen, waarvan geen kweken zijn gedaan, en 12 anderszins heftige lokale reacties. Twee kinderen met encefalopathie zijn gemeld in 2001, beiden na BMR1. Bij één kind werd relatie met de vaccinatie voor mogelijk gehouden, bij het andere stond het beeld los van de vaccinatie.

De zeven sterfgevallen in 2001 gemeld, zijn op één na alle na uitgebreide evaluatie als toevallige samenloop beoordeeld, hoewel niet in alle gevallen een doodsoorzaak kon worden vastgesteld. Eén kind is overleden na de tweede DKTP/Hib vaccinatie waarbij geen enkel postmortaal onderzoek werd verricht; dit sterfgeval kon derhalve niet geclassificeerd worden. De meeste meldingen betroffen simultane DKTP en Hib vaccinaties (1041). BMR was betrokken in 193 van de meldingen, waarvan 47 maal gecombineerd met andere vaccins. In 53% was er een mogelijke causale relatie met de BMR. Voor de andere vaccin(combinatie)s was dit percentage 87%.

Vergeleken met 2000 was er een stijging van het aantal meldingen van 17%. Dit is slechts deels te verklaren uit een groter geboorte cohort (2,5%). De stijging betrof vrijwel geheel de DKTP en Hib vaccinaties en werd vooral gezien bij (onvolledige) collapsreacties en de verkleurde benen na de eerste twee vaccinaties. De rest van de stijging werd gezien in de zogenaamde “minor” beelden, met de overige “major” beelden gelijk aan die in 2000. Mogelijk is dit deels het gevolg van een groter aantal meervoudige meldingen, door intensievere passieve of actieve follow up. Of de stijging (deels) het gevolg is van het gemiddeld beter volgen van het versnelde schema is mogelijk maar blijft speculatief. Er is over 2001 een weer wat grotere spreiding in meldgraad per regio met in de regio's met de hoogste meldgraad relatief meer milde ziektebeelden. Dit zou kunnen wijzen op verminderde onderrapportage om welke reden dan ook. Het totaal aantal mogelijke bijwerkingen moet in relatie gezien worden met het grote aantal verrichte vaccinaties. De grote gezondheidswinst die de vaccinaties van het RVP betekenen, weegt op tegen de mogelijke bijwerkingen.

Summary

Adverse Events Following Immunisation (AEFI) under the Nationel Vaccination Programme (RVP) of the Netherlands have been monitored by the National Institute for Public Health and the Environment (RIVM) since 1962. From 1984 onwards evaluation is done in close collaboration with the Health Council (GR). The 24h-telephone service for reporting and consultation is an important tool for this passive enhanced surveillance system. 96% of reports come in by telephone, in majority from Child Health Clinic staff (90%). Parents, GP's and/or hospital provided additional data on request (78% of cases). RIVM makes a (working) diagnosis and assesses causality after supplementation and verification of data. The assessment is communicated to the reporting party usually by phone (91%). Written assessments, in case of more serious and complicated events, are sent to all medical professionals involved. A committee of GR reassesses a mutually agreed subset of the latter cases and the aggregated results of the others 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 eighth annual report.

In 2001, on a total of nearly 2.5 million vaccinations, 1331 AEFI were submitted, concerning 1251 children. Of these only 17 (1.3%) were not classifiable because of missing information. 82% (1091) of classifiable events were judged to be possibly, probably or definitely causally related with the vaccination and 18% (233) of the events were coincidental.

So-called "minor" local, skin or systemic events were registered in 584 cases of which 425 (74%) were classified as possible adverse reactions in 2001.

Discoloured legs were reported 175 times with a causal relation more or less likely in all but five cases. Other so-called "major" adverse events (categorised under convulsions, collapse, persistent screaming, general major illness and death with inclusion of some skin and local reactions) occurred in 747 cases of which 87% (656) were possible adverse reactions. Collapse, including atypical and incomplete episodes, was diagnosed 268 times, in only 12 cases without causal relation. Five times breath holding spells and 20 times fainting in older children were reported. Convulsions were diagnosed in 56 cases, of which five were non-febrile, with in 79% (50) inferred causality and once non-classifiable. 55 Events were considered atypical attacks, of which 78% (43) with a possible causal relation. Epilepsy (10) was not considered causally related with the vaccinations. All of the 49 reported cases of persistent screaming were considered adverse reactions.

Fever $\geq 40.5^{\circ}\text{C}$ was the working diagnosis in 38 cases of the major illness group, in all but five with inferred causality. Of the other 36 major illness cases ten had a possible causal relation: irritability (1), "vaccinitis" (4), with in three cases also very high fever ($\geq 40.5^{\circ}\text{C}$), and ITP (2), arthritis (1), anaemia (1) and derangement of metabolic disorder (1). The other 26 were considered to be unrelated. There were 13 abscesses, without cultures taken, and 12 other major local reactions.

Two cases of encephalopathy were reported in 2001, both after MMR1. In one case causal relation was considered possible and in the other no relation with the vaccination was established.

In 2001 the seven reported deaths were considered chance occurrences in all but one case, after thorough assessment, with no definite other causes established however. In one case the child died after the second DPTP/Hib vaccination and no whatsoever postmortem investigation has been done. Therefore this case was non-classifiable.

Most frequently reports involved simultaneous DPTP and Hib vaccinations (1041). MMR was involved 193 times, 47 times with simultaneous other vaccines. In 53% of cases there was a possible causal relation with MMR. For the other vaccine combinations this percentage was 87%. Compared to 2000 the number of reports rose with 17%. This is only partly attributable to the larger birthcohort (2.5%). The increase concerned mainly collapse reactions, discoloured legs and pallor in the younger children after the first and second dose of DPTP/Hib vaccinations. Better adherence to the accelerated schedule with on average a younger age at vaccination may play a role but this remains speculative. Some may be due to a greater number of multiple reports as a result of intensified active or passive follow up of prior reports. In 2001 there was an increased dispersion in reporting rate over the different regions with a larger proportion of minor events in the regions with the highest rates and the greatest increase. This suggests decrease in underreporting for whatever reason. The total of 1142 reports should be weighted against the large number of vaccines administered. The risk balance greatly favours the continuation of the vaccination programme.

1 Introduction

Identification, registration, and assessment of adverse events following drug-use are important aspects of post marketing research. Safety surveillance is even more important in the programmatic use of preventive strategies and intervention, especially when young children are involved. In the Netherlands the National Institute for Public Health and the Environment (RIVM) has the task to monitor adverse events following immunisations (AEFI) under the National Vaccination Programme (RVP). Already in 1962, with the introduction of the combined Diphtheria, Tetanus, whole-cell Pertussis and inactivated Polio vaccine (DPTP), a passive surveillance system has been adopted. Since 1984 the safety of the RVP is evaluated in close collaboration with the Health Council (GR). The annual reports of GR limit themselves to advising the Minister of Health on the safety issue of the RVP. By their nature they do not permit comparing rates and types of adverse events between different vaccines, schedules or vaccine lots. The introduction of a vaccine against *Haemophilus influenzae* type b (Hib) coincided with a change in the procedure of registration and assessment of AEFI by RIVM in 1993. The annual reports on adverse events by RIVM are based on the year of notification. They include all reported events, irrespective of severity of symptoms or causal relationship with the vaccination. Reported events are ordered by nature and severity of the symptoms and by causal relation. This 2001 report contains a description of the procedures for soliciting notifications, verification of symptoms, diagnosis according to case definitions, and causality assessment. Notifications were followed with special attention this year because this was the second year in which the new accelerated schedule was applicable for all infants. Towards the end of the year the new booster acellular pertussis vaccine was introduced for all four year-olds (from birth cohort 1998 onwards). We will discuss some specific adverse events and their relation to the vaccination. Special attention will be given to underreporting and to prevention of adverse events and contra-indications and the possible effects of the change in schedule as well as other trends or signals. This RIVM report on adverse events is only issued in English. It includes a detailed description of the background, organisation and procedures of the National Vaccination Programme and the embedding in the Child Health Care System (JGZ).

2 Post Marketing Surveillance

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

Requirements for Post Marketing Surveillance of adverse events have been stipulated in Dutch and European guidelines and legislation ^{3,4}. The World Health Organisation (WHO) advises on monitoring of adverse events following immunisations (AEFI) against the target diseases of the Expanded Programme on Immunisation (EPI) and on implementation of safety surveillance in the monitoring of immunisation programmes ⁵. The WHO keeps a register of adverse reactions as part of the global drug-monitoring programme ⁶. Currently there are several international projects to achieve increased quality of safety surveillance and to establish a register specifically for vaccines and vaccination programmes ^{7,8,9}.

Close evaluation of the safety of vaccines is of special importance for maintaining public confidence in the vaccination programme as well as maintaining motivation and confidence of the health care providers. With the successful prevention of the target diseases, the perceived side effects of vaccines gain in importance ^{10,11}. Not only true side effects but also events with only temporal association with vaccination may jeopardise uptake of the vaccination programme ¹². This has been exemplified in Sweden, in the United Kingdom and in Japan in the seventies and eighties. Commotion about assumed neurological side effects caused a steep decline in vaccination coverage of pertussis vaccine and resulted in a subsequent rise of pertussis incidence with dozens of deaths and hundreds of children with severe and lasting sequelae of pertussis infection ¹³. The diphtheria epidemics in Eastern Europe are also result of anxiety about safety of vaccination (procedures) ¹⁴. But also recently concern about safety rather than actual associations caused cessation of the hepatitis B programme in France ^{15 16}. Even at this moment the uptake of MMR in the UK and the Republic of Ireland is very much under pressure because of unfounded allegations about association of the vaccine with autism and inflammatory bowel disease ^{10,17,18,19,20,21,22,23,24}. Subsequent (local) measles epidemics have occurred ^{25,26,27,28}. In the late seventies of the last century. 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 severe events presented by RIVM. The GR advises the Minister of Health on the safety of the Vaccination Programme with annual reports^{29,30}. Since the GR reports have no direct reference to year of notification or vaccination and contain a selection of reported adverse events they cannot be used for analysis of trends or patterns in reporting of events nor for comparison of vaccines, lots or schedules. The annual reports of RIVM on adverse events aim to contribute to these goals, however, and may lead to specific follow up and systematic study of selected adverse events^{31,32,33,34,35,36,37,38}. We hope this will lead to better understanding of pathogenesis and risk factors of specific adverse reactions. In turn, this may lead to changes in the vaccine or vaccination procedures or schedules and adjustment of precautions and contra-indications and improved management of adverse events. These reports may also serve for the purpose of public accountability for the safety of the programme.

3 The Netherlands Vaccination Programme

3.1 Vaccines and Schedule

In the Netherlands mass vaccinations of children were undertaken from 1952 onwards, with institution of the National Vaccination Programme (RVP) in 1957. From the start all vaccinations covered, were free of charge and have never been mandatory. Although a law existed on smallpox vaccinations, this law has never been enforced. With the eradication of smallpox vaccinations were abandoned and this law was revoked in 1978^{39,40}. At first mono-vaccines against diphtheria, pertussis and tetanus were used and the combined DPT vaccine since 1957. After the polio epidemic in 1956, vaccination against poliomyelitis was added. From 1962 onwards the combined DPTP vaccine, with an enhanced polio component (1978), is in use for vaccination of infants and young children and DTP(olio) for revaccination of older children. Rubella vaccination for 11 year old girls was added in 1974 and measles vaccination for 14 months old children in 1976. In 1987 the combined measles, mumps and rubella (MMR) vaccine replaced the mono-vaccines in a two-dose schedule for all children (14 months and 9 years). Mid 1993 vaccination against (invasive) infection with *Haemophilus influenzae* type b (Hib) was added for children born after April 1st 1993. The actual RVP schedule of 2001 is included in box 1 (appendix 1).

From March 1999 onwards the programme has an earlier start, at two months of age in stead of three. This was decided upon to achieve protection as early as possible for the youngest, most vulnerable children, because of the resurgence of pertussis in the Netherlands. The aim is to have given all children the third dose at five months of age. It was shown that with the prior schedule about one quart of children had not finished their primary series before six months of age⁴¹. For the birth cohort of 1998 an extra pertussis booster vaccination has been included with a single acellular pertussis mono-vaccine (aK), administered simultaneously with the fifth DTP at approximately four years of age⁴².

Box 1. Schedule of the National Vaccination Programme of the Netherlands in 2001

2 months	DTP1 + Hib1
3 months	DTP2 + Hib2
4 months	DTP3 + Hib3
11 months	DTP4 + Hib4
14 months	MMR1
4 years	DTP5*
9 years	DTP6 + MMR2

* aK to be introduced for birth cohort 1998, starting approximately october 2001

DTP, DTP and MMR are produced by SVM/RIVM (currently NVI- Netherlands Vaccine Institute); Hib (PRP-T) vaccine is produced by SVM/Pasteur-Merieuxbut registered in special presentation form by RIVM (currently NVI)(see appendix 2-5). AK is produced and registered by GSK, but filling final bulk into vials is done by SVM. See appendix 6. BCG vaccination is not included in the RVP. Vaccination is however offered to children with higher risk of acquiring tuberculosis when travelling to or staying in countries with a high

prevalence, free of charge. Usually vaccination takes place in the second half-year of life ³⁹. Hepatitis B vaccination (HepB) is available for children of HBsAg positive mothers. This vaccination is given, following HBIg administration at birth, in a four dose schedule at the ages of 2, 3, 4 and 11 months during the regular Child Health Clinic visits, simultaneous with DPTP and Hib. In Amsterdam, with a higher prevalence of HBV carriers, a different schedule and delivery system is operational. Children of refugees and those awaiting political asylum have an accelerated schedule for MMR and are offered catch up doses upto the age of 18 years ³⁹. For the RVP this age limit is 12 years.

From December 1997 onwards the combined DPTP vaccine contains a better-defined pertussis component with on average a higher potency in the mouse protection test. Because of temporary reduced supply MMR from a different manufacturer has been used in the RVP in 1999 and 2000. For the year under report, 2001, only RIVM-MMR has been supplied. Because of some local epidemics of menC infections a small regional vaccination campaign has been organised in 2001. The vaccines were supplied by the government and were free of charge in the designated area ⁴³.

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) ^{39,44}. The PEA is responsible for further distribution to the providers. It also has the task to implement and monitor cold chain procedures at the Child Health Clinics (CB) and Municipal Health Care Service (GGD). The Medical Consultant of the PEA (MAE) guards and promotes programme adherence. The databases of the PEA contain name, sex, address and birth date of all children up till 13 years of age. The databases are linked with the municipal population registers and are updated regularly or on line, for birth, death and migration.

The PEA sends an invitation for vaccination, with a vaccination-registration document and information, to the parents of every child in the second month of life or after immigration. A bar coded card for every scheduled vaccine dose is included. These cards are to be returned to the PEA by the provider after the vaccine is administered. Duplicate cards are available at the vaccination settings. Returned cards are also used for reimbursement of the costs of vaccinating (approx. 5 Euro per vaccine) to the health care organisation. All administered vaccinations are entered in the databases of the PEA on an individual level; the PEA sends reminders to the child's address if necessary. The databases serve also the providers who can check the vaccination status of individual children, or of the population they serve. The data of the PEA follow the child when it moves from one place to another.

The PEA databases also contain results of heel prick tests and of prenatal hepatitis B screening and subsequent vaccinations.

3.3 Child Health Care System

The Child Health Care system (JGZ) aims to enrol all children living in the Netherlands. Child Health Care in the Netherlands is programmatic, following national guidelines with emphasis on age-specific items and uniform registration on the patient charts, up till the age of 18 years ⁴⁰. Up till four years of age (pre school) children attend the Child Health Clinic

(CB) regularly. At school entry the Municipal Health Care Service (GGD) takes over. From then on the Child Health Care gets a more population based approach, with special attention to risk groups and fewer individual check-ups.

The first contact with the family usually occurs less than a week after birth when a nurse visits the home for the heel prick test on phenylketonuria and congenital hypothyroidism (PKU/CHT). At a special home visit approximately two weeks after birth, parents get information on Child Health and an invitation for the first CB visit at one month of age. The nurse may make additional house calls.

In the first year of life about ten CB visits take place during which physical check-ups are performed. These include full medical history and growth and developmental screening at appropriate ages and tests of vision and hearing. Weight, height and head circumferences are recorded on growth charts. Validated test forms are used for developmental follow up. Data on physical examination are also recorded in a standardised form. Parents get advice on food and supplements and information about behaviour, safety issues and upbringing. Interval between visits gets larger as age increases, from four weeks to three months up till the age of 15 months and after that with increasing intervals of three, six and nine months up till the age of four years. The child is seen depending on age specific problems alternating by a nurse or a physician specially trained in Child Health. On individual basis this schedule may be adjusted, and the nurse may make house calls.

The RVP is fully embedded in the Child Health Care system and vaccinations are given during the routine visits. Good professional standards include asking explicitly after adverse events following vaccination at the next visit and before administration of the next dose. The four-year booster shot with DTP is usually given at the last CB visit, before school entrance. Booster vaccination with DTP and MMR at nine years of age is organised in mass vaccination settings, with a possibility for catch up till the age of 13 years. For refugees and asylum seekers the programme covers vaccination up till 19 years of age.

Attendance of Child Health Clinics is very high, up to 99% and vaccination coverage for DTP/Hib is over 97% with a slightly lower uptake for MMR of 95%^{45,46}. (Accurate numbers on birth cohorts 2000 and 2001 have not yet been made available by IGZ).

3.4 Safety Surveillance

Since 1962 an adverse event (AE) surveillance system for the National Vaccination Programme (RVP) has been in effect. It is an enhanced passive reporting system including a 24 hours telephone service. This service is also available for consultation and advice on vaccination matters like schedules, contra-indications and precautions. This permanent availability and easy accessibility of the surveillance system make the reporting channel both fast and direct. AE may also be reported by regular mail, fax or e-mail.

The annually distributed vaccination programme (appendix 1) by the Inspectorate of Health Care (IGZ) encourages Health Care providers to report adverse events to RIVM, giving address, telephone number and fax number. These are also mentioned on the package inserts of the vaccines (appendix 2-6). Most municipal and regional Child Health organisations, which provide the vast majority of vaccinations, have explicit guidelines for notifying AE to

RIVM. The countrywide used guideline book on the RVP with background, execution and procedures, contains a (RIVM written) chapter on possible side effects and gives ample information on notification procedures³⁹. RIVM promotes reporting through information, education and publications, for instance by contributing to refresher courses for Child Health Clinic staff. Family physicians and paediatricians are informed at symposia and lately also during their training. Feedback to the reporter of AE and other involved professionals has been an important tool in keeping the reporting rate at high levels.

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

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

- | |
|--|
| <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 RIVM, irrespective of nature and severity of symptoms, diagnoses or time interval. No discrimination is made for official reports or consultations regarding adverse events. After receipt of a notification, a physician of RIVM reviews the information. Data are verified and the need for additional information is established. Additional information may be obtained from clinic staff, parents, general practitioners and hospital. Also data from the PEA are collected. Upon verification of symptoms and completion of data a (working) diagnosis is made. Interval with the vaccination and duration of the event is established and causality assessed. The feedback includes a description of verified symptoms, diagnosis and causality assessment by RIVM, and advice on subsequent vaccinations. See for detailed description on procedures chapter 5. Since 1984 the Health Council (GR) re-evaluates reported AE on the basis of formal detailed written assessments by RIVM. These written assessments include the more serious reported events. Criteria for selection of the cases to be presented to GR have been mutually accepted. The other reports are cross-checked sample wise by GR. Since 1994, for reasons specified in chapter 2, RIVM makes an annual report on adverse events and no longer reports indirectly via reports by GR only. For further details see paragraph 5.7.

4 Materials

4.1 Post Vaccination Events

Events following immunisations do not necessarily have a causal relation with the vaccination and some have a temporal association only and are in fact merely coincidental^{10, 11,44}. 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; generally only events within 28 days of vaccination are regarded as potential side effects for killed or inactivated vaccines and for live vaccines this risk window is 6 weeks. For some disease entities a longer risk period seems reasonable.

Following are some definitions used in this report.

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

Adverse events are thus divided in coincidental events and genuine side effects. Side effects are further subdivided in vaccine or vaccination intrinsic reactions, vaccine or vaccination potentiated events, and side effects through programmatic errors (see box 3)^{47,48,33,34}.

Box 3. Origin / Subdivision of adverse events by mechanism

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

4.2 Notifications

All incoming information on adverse events following immunisations (AEFI) under RVP, whether reports or requests for consultation about cases are regarded as notifications. All notifications are recorded on an individual level. For notifying and information a 24-hr telephone service is available. This permanent availability with instant consultation and advice makes this notification channel direct, easily accessible and fast, resulting in high

quality of data. Notifications are also received by letter, form or fax. For further details see paragraphs 3.3 and 3.4 and chapter 5 on methods.

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

Box 4. Subdivision of notifications of adverse events following vaccinations

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

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

5 Methods

5.1 Analysis

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

5.2 Additional Information

Necessary data on vaccines, symptoms, circumstances and medical history are usually obtained in the notifying telephone conversation with the reporter, usually Child Health Clinic staff. They (should) 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 GP or hospital are contacted. As is often the case, anxiety, confusion or missing data, makes it necessary to take a full history from the parents who are asked to provide a detailed description of the adverse event and circumstances. If needed permission to request information from medical records is obtained also. This interview is mostly taken by telephone but rarely nowadays a physician of RIVM visits parents at home or at the 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 RIVM. Minor difficulties in assessment may lead to ad hoc consultations and discussions to arrive at consensus.

5.4 Causality Assessment

Once it is clear what exactly happened and when, and predisposing factors and underlying disease and circumstances have been established, causality will be assessed³⁴. This requires

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

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

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

The nature of the vaccine and its constituents determine which side effects it may have and after how much time they occur. For different (nature of) side effects different time limits/risk time may be applied. Causal relation will then be appraised on the basis of a checklist, resulting in an indication of the probability/chance that the vaccine is indeed the cause of the event. This list is not (to be) used as an algorithm although there are rules and limits for each point of consideration (see box 5).

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

Certain (conclusive, convincing, definite), if the vaccine is proven to be the cause or if other causes are ruled out definitely; there should be a high specificity of the symptoms and a fitting interval. *Probable* causal relation, if there are no signs of other causes, but a fitting interval and a satisfactory biologic plausibility of vaccine/vaccination as cause of the event. If, however, there are other possible causes or the time interval is only just outside of the acceptable limits or symptoms are rather unspecific the causal relation is classified as *possible*. If a certain, probable or possible causal relation is established, the event is classified as adverse reaction or side effect.

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

Box 6. Criteria for causality categorisation of AEFI

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

Generally it is considered as well to what extent the vaccine or vaccination has contributed to the event and how. This is especially important in case faulty procedures are involved. This may have implications for management of side effects or contraindications. See also paragraph 4.1 and box 3.

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

5.5 Event Categories

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

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

- Faints: Collapse reactions (HHE, Hypotonic hyporesponsive Episode), a sudden loss of consciousness, loss of muscle tone and pallor, are included unless these symptoms are explicable as post-ictal state or part of another disease entity. If symptoms are incomplete or atypical this is added as an annotation. In collapse following fierce crying that suddenly stops with or without the clear-cut breath holding phase, annotation will be made too. In case of classical breath holding spell with no or very short white phase this event will be listed under faints as a separate group. Fainting in older children is listed as a separate group within this category. Just pallor or apathy or prolonged sleeping or limpness is not considered collapse reaction.
- Fits: Convulsions are all episodes with tonic and/or clonic muscle spasms and loss of consciousness. There is discrimination by body temperature in non-febrile and febrile convulsions. If fever is $\geq 38.5^{\circ}\text{C}$ it is booked as febrile convulsion unless the convulsion is symptomatic for meningitis or for other illness. Febrile seizures of more than 15 minutes or asymmetrical or recurring within 24 hours are complex as opposed to simple (classic). Definite epileptic phenomena are included in this category also. Unspecifiable atypical attacks are a separate group under fits. These are paroxysmal occurrences without the specific criteria for collapse or convulsions. Nocturnal myoclonics are not included, neither are episodes of irritability, jitteriness or chills; these are grouped under general illness.
- Encephalitis or Encephalopathy: children younger than 24 months with encephalopathy have an explicit or marked loss of consciousness for at least 24 hours which is not caused by intoxication and not explicable as post-ictal state. In children older than 24 months at least 2 of the 3 following criteria must be fulfilled:
 - distinct change in mental status as disorientation, delirium or psychosis not caused by drugs;
 - marked decrease in consciousness not caused by seizures or medication;
 - seizures with (long lasting) loss of consciousness.Also signs of increased intracranial pressure may be present. In encephalitis, apart from the symptoms of encephalopathy there are additional signs of inflammation as fever and elevated cell counts in the cerebrospinal fluid.
- Anaphylactic Shock: Circulatory disturbance with hypotension and life threatening hypoperfusion of vital organs. This reaction should be in close temporal relation with intake of an allergen and with type I allergic mechanism involved. There may be accompanying laryngeal oedema or bronchospasm. Urticaria or wheezing alone is not included.
- Death: all reported children who died following immunisation are included in this category and not under one of the other listed categories.

Box 7. Main event categories with subdivision according to severity

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

5.6 Recording, Filing and Feedback

Symptoms, (working) diagnosis, event category and assessed causal relation are recorded on the notification file together with all other information about the child, as medical history or discharge letters. Severe and other important events are discussed in the periodic clinical conference among the physicians of RIVM, before final assessment, critical reviewing from different angles in order to reach consensus; of this annotation is included in the file. All notifications are, after completion of assessment and feedback, coded on a structured form for future aggregated analyses and annual reports. This coding is entered in the logbook in which all incoming adverse events are entered on the date of notification. A single physician does all the coding in order to achieve maximal consistency. This way there is of every notification a time spaced second appraisal. If there are discrepancies, the assessment is discussed with the original appraiser or a colleague. If there is new follow-up information, the case is reassessed 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 feedback forms may be used, including listed verified symptoms, diagnosis and causality assessment with added advice, for most notifications that now get a full written report. The full written reports will be reserved for

selected cases to be re-evaluated by the GR committee or offered for second opinion to this committee. A project has been started for a database application, which allows for both feedback and aggregated analysis (see paragraph 5.8).

5.7 Health Council

Since 1984 the Health Council (GR) advises the Minister of Health on the safety of the National Vaccination Programme. A permanent committee has been appointed. Currently this expert group includes specialists on the following (different) fields: paediatrics, child health care, public health, epidemiology, microbiology, neurology, immunology, pharmaco-vigilance, pathology, vaccinology. GR base their safety advice mainly on the re-evaluation of the formal written assessments by RIVM and other available information on the anonymised cases. Together with data from the international medical literature and the aggregated reports of all notifications assessed by RIVM, the final judgement on the safety of the programme is reached. Physicians of RIVM are advisory members of this GR committee. Annually, GR makes a working visit to RIVM to audit the proper procedures and the completeness of registration and the quality and consistence of assessments.

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

Because the workload of the committee had to be reduced and assessment criteria have been agreed upon, only a selection of listed events are reassessed from 1996 onwards, with review of summarised reports of the other events. For the year under report (2001) this change in procedure did have impact on the number of written reports by RIVM and reassessed cases by GR. The committee will include her reassessments in the annual advice to the Minister of Health. A redefining of the task of this permanent committee is at hand, since the safety surveillance as off 2002 will be independent from the manufacturer of vaccines. The planned reallocation of the vaccine department of the RIVM together with SVM as separate vaccine manufacturer, cut loose from the RIVM, makes the necessity of secondary independent reassessment by GR less obvious. The broader scientific discussion of particular possible adverse effects within this GR committee will however add to value of the safety surveillance.

5.8 Annual Reports and Aggregated Analysis

The coded forms are used as data sheets for the annual reports. For 2001 all reported events have been coded by one of us (PEVdB), after reappraisal of the information. Grouped events were checked for maximum consistency. Samples of final diagnosis, causality and categorisation have been discussed in the training programme of new investigators. The development of a robust database is behind schedule; therefore the data for this report have been entered in a temporary database with limited possibilities. Trend analysis as planned and more in-depth evaluation will have to wait until the new system is installed.

5.9 Quality Assurance

Assessment of adverse events is directed by a standard operating procedure (12N-GCP-08). There has been an internal inspections up till 2001 and the GR regular audit over the year 2001/2002. This will be commented upon in the GR report over 2001/2002.

6 Results

6.1 Number of Reports

In 2001 RIVM received 1322 notifications of adverse events, on a total of nearly 2.5 million vaccinations (Birth cohorts 203,469 in 1999 and 208,521 in 2000 according to the PEA registers and 201,748 for 1999 and 207,097 and 204,039 for 2000 and 2001 respectively according to CBS)^{45,46,49}. Nine notifications were compound with two distinct adverse events after one vaccination date. This annual report thus contains 1331 reported adverse events. These reports involve 1251 children, compared to 1088 children in 2000. There were 65 children with multiple reports, of which five concerned three different vaccination dates and once one of the multiple reports was also compound. Multiple and compound reports are listed under the respective event categories. In 1998, 1999 and 2000 there were 26, 44 and 40 multiple reports and nine, eight and 13 compound reports with a total of 1100, 1197 and 1142 reports, respectively. As described in paragraph 4.2, notifications concerning more than one vaccination date with only mild or common symptoms were booked as single reports unless reported on different dates (table 1).

Table 1. Type of reports of notified AEFI in 2001

notifications	children	adverse events
single	1178 ^a	1178
multiple	64 ^b	133
compound	8	16
compound and multiple	1	4
total	1251	1331

^a 32 children with reports in previous (18) and/or following years (10); these are not included

^b five triple reports

From 1994 onwards comparisons of numbers are valid because the criteria for recording have been consistent, criteria for events eligible for written assessments have changed however. Even without exact counts of former years, it is clear that the number of reported events increased in 1994 and 1995 with levelling off in 1996 and 1997 (table 2). This was considered to be due to decreased underreporting. In 1998 there was a significant increase in the number of reports judged to be partly due to increased awareness and apprehension, further reduced underreporting and possibly to some increase in actual adverse reactions as well ³⁴. In 1999 there was again an increase in number of reports. This was to be expected because the change in schedule from march 1999 onwards resulted in a larger number of vaccinated infants of about one month cohort with for dose 1, 2 and 3 approximately an extra 50,000 DTP/Hib vaccinations. Any change in the programme may give rise to increased apprehension and awareness, which might in turn lead to an increase in notifications also. There appears to be a gradual increase in the birth cohort also. (See reports on 1998, 000001004, on 1999, 000001005 and on 2000, 000001006 www.rivm.nl). In the current year there is again an increase in reported adverse events i.e. 17% more reported events in 15% more children compared to 2000. We will go into this in the the following paragraphs and in the discussion.

As in previous years the notification rate is not even over the months, range 83-148, with again the lowest rate in winter.

Table 2. *Number of reported AEFI per year*

year of notification	written assessments ^a	total ^b
1984	91	310
1985	139	325
1986	197	350
1987	149	325
1988	143	390
1989	141	440
1990	128	375
1991	136	340
1992	147	440
1993	227	496
1994	276	712
1995	234	800
1996	141	732
1997	76	822
1998	48	1100
1999	74	1197
2000	65	1142
2001	116	1331

^a before 1994 registration according to year of vaccination and from 1994 onwards to year of notification

^b up till up till 1993 total numbers are estimates; from 1994 onwards totals are accurate counts

6.2 Reporters

The first person to notify RIVM about an adverse event is the reporter. As in previous years the vast majority of reports were made by telephone (table 3). Only 41 notifications came by regular mail, most frequently as regionally used, special report forms and some as (hospital discharge) letter. Also some reports came in by E-mail (3) or fax (6). Over the last eight years the absolute number of written notifications fluctuates a little between 25 and 51. Reports

from Child Health Clinics accounted for 81% (varying between 78 and 84% over the years). The increase in reports is predominantly from the clinics.

Table 3. Source and reporting route of AEFI in 1994-2001

		1994	1995	1996	1997	1998	1999	2000	2001	tel	mail
Clinic staff ^a	Physician	474	548	466	547	678	722	687	794	764	30 ^b
	Nurse	78	102	116	142	219	221	199	290	285	5
Paediatrician		60	59	56	39	69	70	80	56	52	4
General Practitioner		25	13	26	20	35	34	28	18	18	-
School Health Service		15	18	17	10	31	27	37	31	30	1
District Consultant		9	18	11	16	15	16	5	11	10	1
Parent		25	34	35	40	52	91	97	115	112	3
Other		5	6	2	7	1	9	7	14 ^c	8	6
Unknown		21	2	3	1	-	7	2	2	2	-
Total		712	800	732	822	1100	1197	1142	1331	1281	50

^a including staff of refugee clinics (10)

^b including three email reports

^c including reports bij Lareb (6), labs (3), pharmacists (4) and KNCV (1)

The parents of 115 (8.6% compared to 8.5% in 2000) children reported directly themselves; mostly they were advised to do so by clinic staff. Over the years there has been a slow steady increase from 3.5% in 1994 to 8.5% in 2000. Absolute numbers of parental reports are increasing from 1994 onwards. The other notification sources were more or less stable. We failed to note the reporting source in two cases. See also paragraph 6.6 for information sources.

6.3 Regional Distribution

Reports come from all over the country, but are not evenly spread. Standardisation of the rate per 1000 vaccinated infants is done according to the data from the PEA³². In table 4 the rates for 1999 and 2000 have been adjusted since the coverage data for 1999 have been made available by IGZ^{45,46}. Like before we use the coverage data for the first three DPTP doses. Compared with the approximation in the previous reports there are only minor differences, with slightly lower reporting rates for 1999 (5.6 in stead of 5.7) The accurate data for 2000 and 2001 are not available yet therefore coverage data for 1999 have been used. For 1999 this new estimation was again adjusted with an approximation of the average increase of vaccinated infants per region caused by the change in schedule. Since the regular summarised reports of coverage data do not contain information on timing of the vaccination there will remain inevitable inaccuracies in estimated rates per region for this year.

Table 4. Regional distribution of reported AEFI in 1994-2001, per 1000 vaccinated infants^a with proportionate confidence intervals

	1994	1995	1996	1997	95% c.i.	1998	95% c.i.	1999 ^b	95% c.i.	2000(major)	95% c.i.(major)	2001(major)	95% c.i. (major)
Groningen	3.1	4.3	3.5	2.7	1.4-4.0	5.3	3.5-7.1	5.1	3.5-6.8	5.5 (3.7)	3.7-7.4 (2.2-5.2)	4.5 (3.4)	2.8-6.1 (2.0-4.8)
Friesland	2.5	4.7	3.6	4.6	3.1-6.1	5.1	3.5-6.7	6.0	4.4-7.6	5.6 (3.7)	4.0-7.2 (2.4-5.1)	6.6 (3.2)	4.8-8.4 (2.0-4.5)
Drenthe	1.8	2.0	3.2	2.7	1.3-4.1	5.8	3.9-7.7	4.4	2.8-6.1	4.6 (2.5)	2.9-6.3 (1.2-3.7)	3.6 (2.0)	2.1-5.2 (0.9-3.1)
Overijssel	2.1	4.0	2.7	4.0	3.0-5.1	4.6	3.5-5.8	4.9	3.8-6.0	6.5 (3.2)	5.2-7.9 (2.3-4.2)	6.2 (3.4)	4.9-7.5 (2.4-4.3)
Flevoland	1.4	3.4	2.6	2.5	1.1-3.9	3.9	2.2-5.8	2.4	1.6-3.7	4.7 (3.0)	2.8-6.5 (1.5-4.4)	6.9 (4.1)	4.7-9.1 (3.0-5.8)
Gelderland	2.9	4.0	3.5	3.9	3.1-4.7	5.2	4.3-6.2	4.4	3.6-5.2	4.9 (2.9)	4.1-5.8 (2.2-3.6)	5.2 (3.0)	4.3-6.1 (2.3-3.7)
Utrecht	4.6	4.2	4.4	5.0	3.8-6.4	6.7	5.4-8.0	6.6	5.4-7.9	5.2 (2.5)	4.0-6.3 (1.7-3.4)	7.0 (3.6)	5.7-8.4 (2.6-4.5)
Noord-Holland ^c	2.4	3.8	3.9	4.3	3.4-5.1	4.7	3.8-5.6	4.0	3.2-4.8	5.7 (3.6)	4.7-6.7 (3.0-4.3)	5.2 (2.8)	4.3-6.1 (2.1-3.5)
Amsterdam	8.2	6.0	4.4	5.9	4.3-7.5	7.2	5.5-9.0	5.6	4.1-7.1	5.4 (2.6)	3.8-6.9 (1.5-3.6)	8.3 (3.7)	6.4-10.2(2.4-5.0)
Zuid-Holland ^c	4.6	5.0	4.5	4.8	4.0-5.6	6.1	5.2-7.0	6.4	5.5-7.3	5.7 (3.1)	4.8-6.6 (2.5-3.8)	7.6 (4.0)	6.6-8.6 (3.3-4.7)
Rotterdam	4.1	5.4	3.1	4.6	2.9-6.2	3.8	2.3-5.3	3.8	2.4-5.2	5.3 (3.1)	3.6-7.0 (1.8-4.4)	5.5 (3.8)	3.7-7.2 (2.4-5.3)
Den Haag	6.0	3.0	7.3	6.4	4.2-8.6	11.0	8.1-14.0	9.4	6.9-11.9	7.2 (4.4)	4.9-9.4 (2.7-6.2)	9.4 (3.8)	6.8-12.0(3.3-7.1)
Zeeland	1.2	2.5	2.2	2.9	1.3-4.5	4.0	2.1-5.9	3.5	1.8-5.2	5.7 (3.8)	3.4-8.0 (1.9-5.7)	7.8 (5.2)	5.2-10.5(3.6-8.2)
Noord-Brabant	3.3	3.7	4.3	4.1	3.4-4.9	5.3	4.5-6.1	6.7	5.8-7.6	6.6 (3.3)	5.6-7.5 (2.6-4.0)	7.9 (4.5)	6.9-8.9 (3.7-5.2)
Limburg	3.4	4.2	3.4	5.3	4.0-6.6	6.2	4.8-7.5	7.0	5.6-8.4	6.2 (3.9)	4.8-7.5 (2.8-5.0)	8.4 (5.4)	6.8-10.1(4.1-6.7)
Netherlands ^e	3.6	4.2	3.9	4.3	4.0-4.6	5.6	5.2-5.9	5.6	5.3-5.9	5.7 (3.2)	5.4-6.1 (3.0-3.5)	6.7 (3.8)	6.4-7.1 (3.5-4.0)

^a uptill 1999 accurate coverage data are used as published by the Inspectorate of Health Care. Data for 1999 and 2000 have been adjusted accordingly. For 2000 and 2001 coverage data for 1999 have been used.

^b for 1999 figures are adjusted with approximation of higher number of vaccinated infants because of change in schedule.

^c provinces without the three big cities (Amsterdam, Rotterdam, Den Haag)

^d the Netherlands have a birth cohort of approximately 205.000 per year and vaccination coverage of 97% on average for the first three dptp/hib vaccinations.

^e excluding a few children residing in foreign countries and with unknown habitat

The birth cohort increased from a little below 190,000 in 1996 to 208,521 in 2000 (with according to CBS an small decrease in 2001, CBS site per september 2003)⁴⁹. Comparing the different regions in 2000 and 2001 does show an increase in rates, and the difference in the overall rates of 5.7 and 6.7 is statistically significant. See table 4 and figure 1. Reporting rates for only the so-called major events show a smaller increase compared to 2000. See figure 1. We will go into differences in numbers of specific events in the respective paragraphs. For 2001 there was a little more dispersion of the reporting rates over the different regions with a less even distribution than in 2000. For the major events only the differences were also smaller.

for 1999 rates are based on birth cohort 1998 with approximation of increase in vaccinated infants because of the change in schedule to an earlier start.

@ for 2000 and 2001 the coverage data of cohort 1999 have been used since coverage data for the cohorts 2000 and 2001 have not yet been made available.

* provinces without big cities Amsterdam, Rotterdam, Den Haag

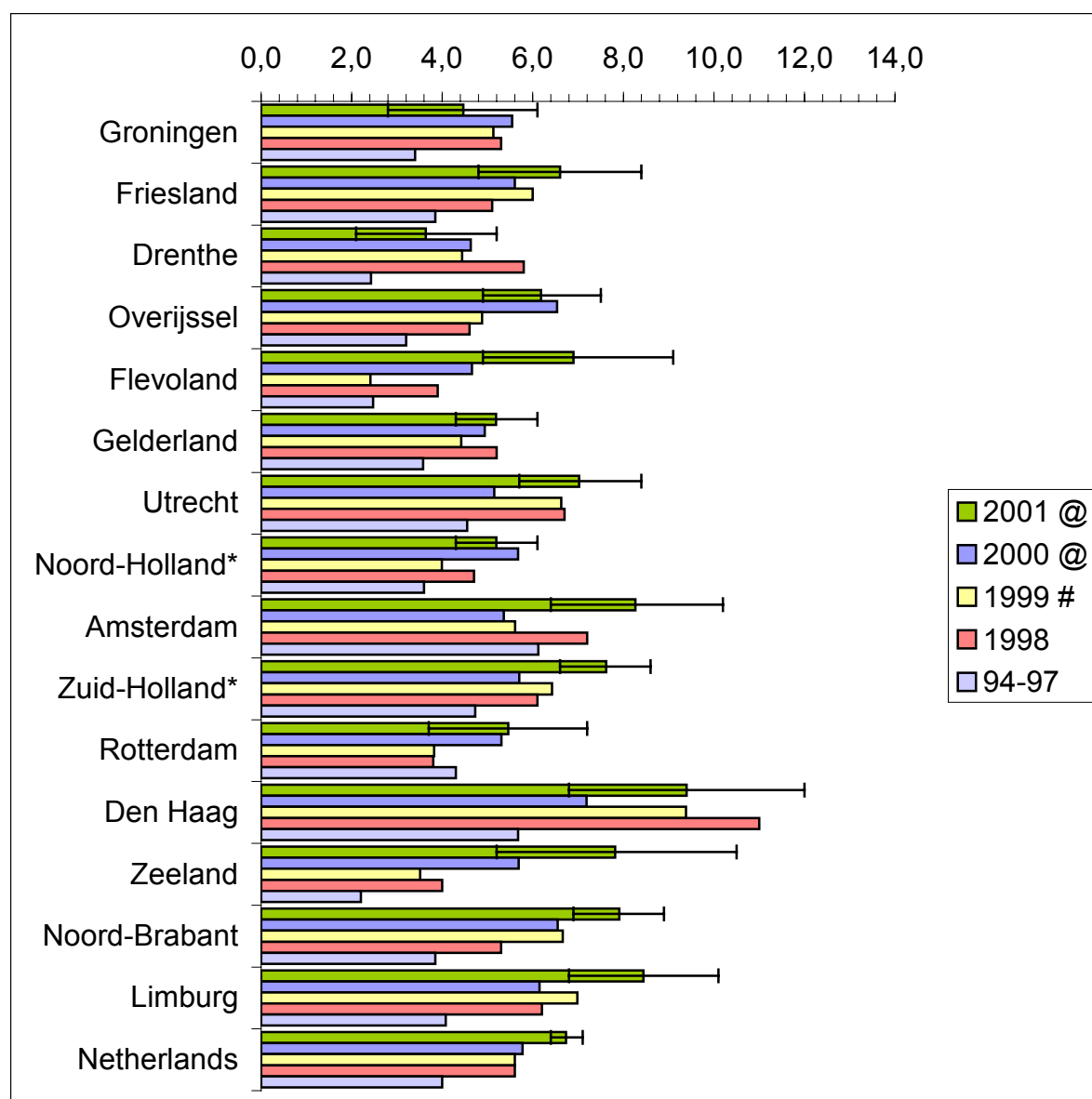


Figure 1. Number of reported AEFI in 1994 till 2001 per 1000 vaccinated infants (with 95% confidence interval bars, proportional, normal approximation)

6.4 Vaccines

In 2001 most notifications were about recent vaccinations, all except 25. These latter notifications arose from concerns about planned booster vaccination or vaccination of younger siblings; in over half of these cases parents called. The vaccine involved in these late reports was often MMR (9). All reports are included in the tables.

In table 5 scheduled vaccines and actually administered vaccines are listed. As in prior years, reports on the first DPTP/Hib dose were the most prevalent (515), with declining numbers on subsequent vaccinations and older age, respectively 229, 163, 172 for second, third and fourth dose. See for relative frequencies of involved vaccine doses figure 2. For actually simultaneous DPTP/Hib vaccinations (1033) numbers were much higher than in previous years with 882 reports concerning DPTP/Hib in 2000 (increase of 17%). The increase was greatest for the first three doses. For all other vaccines and combinations the numbers are similar to 2000. In 28 reports DPTP was given singly (22, 20 and 16 in 1998, 1999 and 2000), without simultaneous other vaccines. 11 Children received a single Hib vaccination. Only one report concerned DPTP/Hib with simultaneous HepB vaccination. Two children received DTP(olio) instead of the scheduled DPTP by parental choice or fear because of prior adverse events (in siblings).

Table 5. Schedule and vaccines of reported AEFI in 2001

vaccine given⇒ scheduled ↓	dtp	dtp hib	hib	dtp hib mmr	dtp mmr	mmr	dtp	dtp aK	dtp mmr	menC	other	total 2001	2000	1999	1998	1997	1996	1995
dtp1+hib1	3	510 ^a	2	-	-	-	-	-	-	-	-	515	418	394	372	323	284	324
dtp2+hib2	7	221	1	-	-	-	-	-	-	-	-	229	191	227	205	142	139	141
dtp3+hib3	4	156 ^b	3	-	-	-	-	-	-	-	-	163	133	166	148	103	96	103
dtp4+hib4	12 ^c	144 ^d	5	8 ^e	1	-	2 ^f	-	-	-	-	172	166	188	148	95	88	83
dose?	1	2	-	-	-	-	-	-	-	-	-	3	6	8	14	7	4	9
mmr0	-	-	-	-	-	4	-	-	-	-	-	4	4	-	-	-	-	-
mmr1	-	-	-	-	-	139	-	-	-	-	-	139	141	139	139	98	80	95
dtp5	1 ^g	1 ^h	-	-	1 ^j	-	30 ^k	7	1 ^l	-	-	41	33	35	34	22	24	18
dtp6+mmr2	-	-	-	-	-	3	8 ^m	-	36 ⁿ	-	-	47	49	33	33	25	13	21
other	-	-	-	-	-	-	-	-	-	5 ^o	13 ^p	18	1	7	7	7	4	6
total 2001	28	1034	11	8	2	146	40	7	37	5	13	1331	1142	1197	1100	822	732	800

a once dtp/hib with simultaneous hepB; once dtp/hib2

b once simultaneous RSV monoclonal antibodies (synagis)

c three times dtp2 and once dtp3

d once dtp/hib1 and twice dtp/hib3

e once with simultaneous bcg

f twice dtp2, late start and primary choice

g dtp2

h dtp/hib1

j dtp1/mmr1

k once dtp1, once dtp2 and once dtp4

l with simultaneous mmr1

m five times catch up doses in refugees

n four times together with catch up mmr1

o once with simultaneous 7-valent pneumococcal vaccine

p four times bcg, three times influenza, twice tetanus, once hepB, once hepB and hepA, once typhoid fever and once dpt and opv in foreign country

Seven children were reported who were vaccinated with acellular pertussis vaccine simultaneously with their DTP booster at four years of age. This vaccine is introduced as booster dose in the programme as off approximately October 2001 for birth cohorts 1998 and after. Five children were reported with adverse events after MenC vaccination, once with

simultaneous pneumococcal conjugate vaccine. None of these were part of the outbreak control in the small local campaigns that were organised in 2001.

13 Children were reported with adverse events following other non-RVP vaccines. See for further details table 5. The step up in reports on adverse events following MMR1 has been judged decreased underreporting³⁴.

In 2001 MMR was involved 192 times of which 146 concerned a single dose of MMR of which four times before the age of one year. (For 2000 these figures were 192, 149 and six, respectively.) Three children received a single MMR dose at school age (versus four in 2000). In ten cases MMR was given with simultaneous DTP with or without Hib (versus six in 2000), once with BCG just before. 36 Times, equal to 2000, MMR was given simultaneously with DTP in the regular schedule at school age with four times MMR1. One child was given his first MMR with DTP5 at four years of age.

41 Reports concerned the fourth-year dose compared to 33 in 2000. Single DTP (booster) was involved 30 times and another 7 times with simultaneous aK and the one child with simultaneous MMR1. Three children got catch up doses with DTP at four years once with MMR1 and once with Hib1.

Reports concerned (re)vaccination at school age 47 times (versus 49 in 2000), of which three times MMR only, eight times DTP only (mainly catch up doses).

Table 6. Event category and (scheduled) vaccine dose of reported AEFI in 2001

event ↓	vaccine→*	dtp/hib 1	dtp/hib 2	dtp/hib 3	dtp/hib 4	dtp/hib ?	mmr 0 or 1	dtp 5	dtp6/ mmr2	other	Total 2001	2000	1999	1998	1997	1996	1995
local reaction		19	5	12	23	2	-	11	13	5	90	75	89	69	49	46	39
general illness	minor	158	65	56	66	31	63	16	15	7	447	366	373	405	254	244	280
	major	11	6	13	21	-	20	-	1	2	74	106	111	85	57	51	55
persistent screaming		39	7	2	1	-	-	-	-	-	49	39	34	29	26	16	22
skin symptoms		19	11	5	11	-	16	4	6	1	73	75	85	75	74	58	61
discoloured legs		80	59	28	6	-	-	2	-	-	175	126	130	125	95	99	93
faints		175	61	30	7	-	-	7	12	1	293	239	244	174	155	134	147
fits		14	13	17	36	-	39	1	-	1	121	112	123	133	108	73	97
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		-	-	-	-	-	2	-	-	-	2	1	1	-	1	2	1
death		-	2	-	1	-	3	-	-	1	7	3	7	5	3	9	5
total 2001		515	229	163	172	3	143	41	47	18	1331	1142	1197	1100	822	732	800

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

Event categories are not equally distributed over the (scheduled) vaccinations (table 6).

Faints, mainly collapse, and discoloured legs are most often reported after the first vaccinations, as is persistent screaming. This is consistent over the years.

Convulsions, especially febrile, are reported more frequently after the fourth DTP/Hib and the first MMR, than at younger ages.

No children with anaphylactic shock were reported and two cases of (possible) encephalopathy/encephalitis after MMR. Seven children who died were reported. Consult for details the paragraphs on causality and the specific events. Compared to 2000 numbers have gone up (17%). Reports on discoloured legs showed the greatest relative increase of 39% (49)

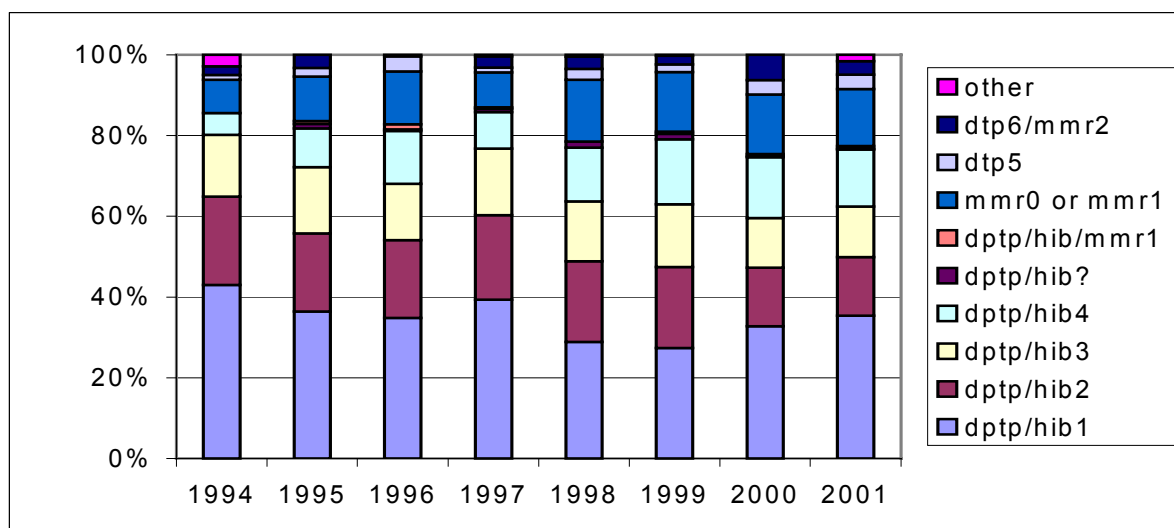


Figure 2. *Relative frequencies of vaccine doses in reported AEFI in 1994-2001*

and persistent screaming rose 26% (10) with collaps increasing 23% (54). For the largest category of general illness (combined for major and minor) the absolute number rose 49 amounting to an increase of 10%. All reported events are included in the numbers in table 6, irrespective of causality. See for degree of causality paragraph 6.8, and also details about specific events under paragraphs 6.9. The relative frequency of the different event categories is more or less the same over the years (figure 3). General illness is the largest category over the years, with a relative frequency of around 40%. For major general illness, not necessarily

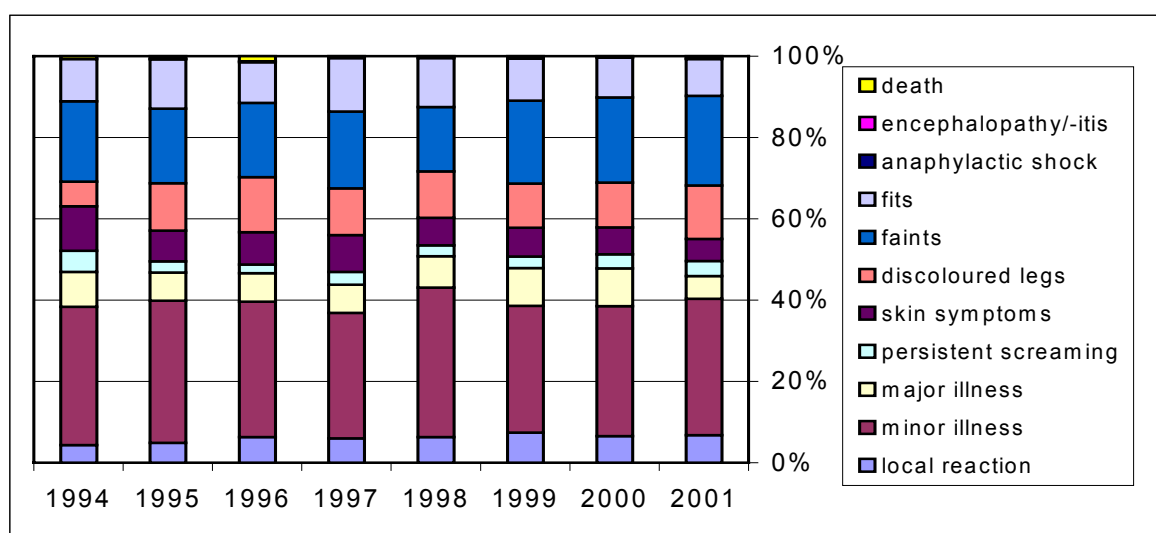


Figure 3. *Relative frequencies of events in reported AEFI 1994-2001*

causally related, the frequency varies a little over the years and after the nine percent in 1999 and 2000 went down a little in absolute numbers and in relative frequency. For fits and skin symptoms the relative frequency goes perhaps a little down also.

The age distribution is again given in figure 4, comparing 1998 under the old schedule and 2000 and 2001, reflecting the new schedule in the age of the reported children. The current

database of the PEA does not allow a precise distribution curve of age at vaccination for the different vaccines for the denominator, only month of vaccination is registered.

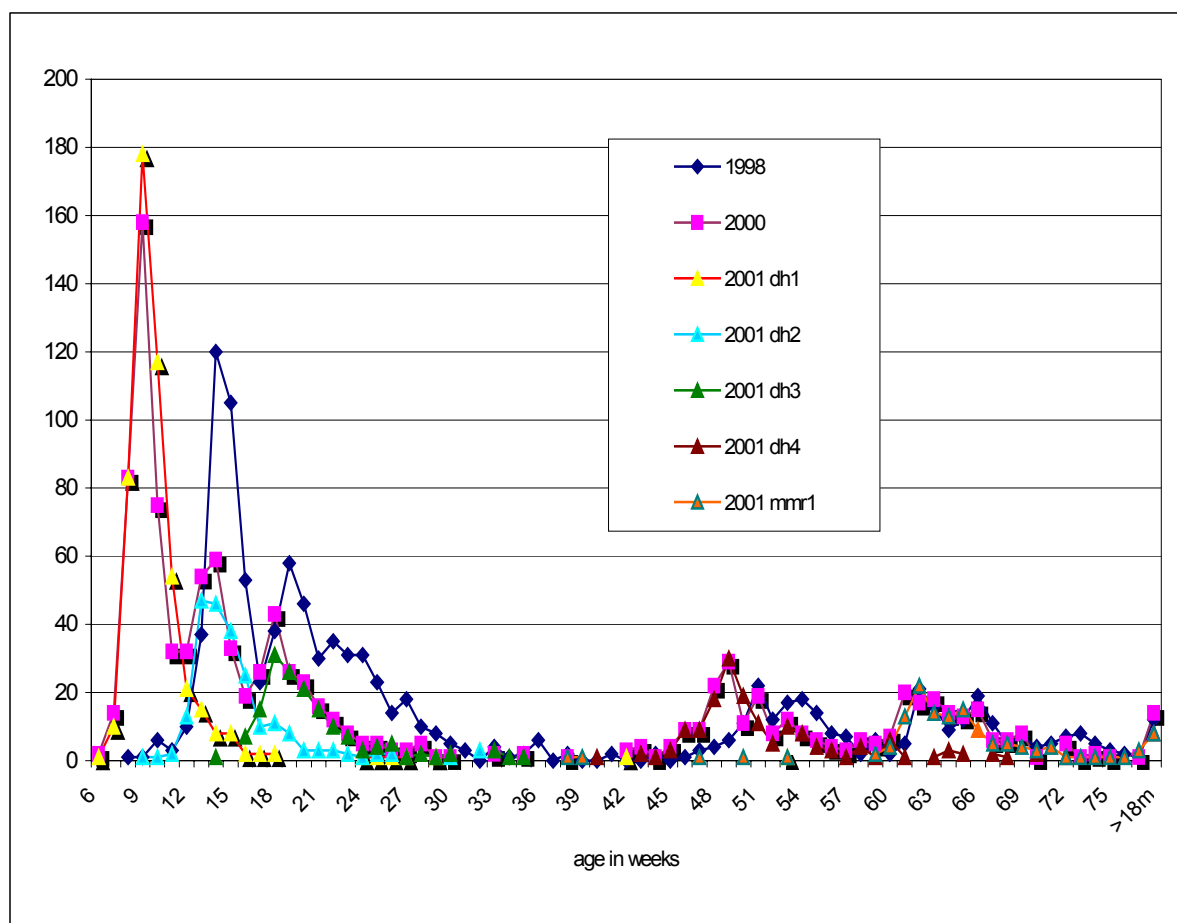


Figure 4. Age distribution of reported AEFI in 1998, 2000 and 2001

6.5 Feedback to Reporters

Feedback of diagnosis and causality assessment with advice about further vaccinations is a major characteristic of the surveillance system. In about one third of the reports this is (preliminarily) achieved in the notifying phone call. And in about another 10-15 percent final assessment did not change the preliminary evaluation substantially. In over half of the reports however cases could only be assessed after further verification and additional information. In over one third of notifications the original information lacked essential data. In about one third of the reports the notified diagnosis and/or involved vaccines or time intervals needed adjustment. The feedback, for these reports also, is increasingly done by telephone due to a change in procedures (in 1996) and lack of a robust database system and manpower. The intent is to supply a comprehensive written feedback with assessment routinely. In 2001 9% of reports got a full written assessment, equal to 2000 and 1999 with an increase in actual numbers.

Table 7. *Feedback method and events of reported AEFI in 1997-2001*

event ↓ feedback method ⇒	written	tel	1997 total	written	tel.	1998 total	written	tel.	1999 total	written	tel.	2000 total	written	tel.	2001 total
local reaction	-	49	49	-	69	69	-	89	89	3	72	75	1	89	90
general illness minor	3	251	254	4	401	405	5	368	373	8	358	366	21	426	447
major	16	41	57	14	71	85	21	90	111	18	88	106	14	60	74
persistent screaming	-	26	26	-	29	29	-	34	34	-	39	39	2	47	49
skin symptoms	4	70	74	1	74	75	2	83	85	-	75	75	0	73	73
discoloured legs	4	91	95	1	124	125	9	121	130	5	121	126	14	161	175
faints	20	135	155	9	165	174	18	226	244	17	222	239	34	259	293
fits	25	83	108	14	119	133	11	112	123	15	97	112	22	99	121
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	0	0	-
encephalopathy/-itis	1	-	1	-	-	-	1	-	1	1	-	1	2	0	2
death	3	-	3	5	-	5	7	-	7	3	-	3	7	0	7
total	76	746	822	48	1052	1100	74	1125	1197	70	1072	1142	116	1215	1331

6.6 Source of Information and Medical Intervention

In a little over one fifth of the notifications the reporter was the sole informan and in 78% information was received from others also, both spontaneously and requested, a rise of 10% compared to 2000 and 1998 (table 8). In 94% of the reports the clinics (child health care, school health and refugee clinics) supplied information. Parents were in 80% (1069) of cases contacted, sometimes during the notifying telephone call at the Child Health Clinic.

Table 8. *Information sources and events of reported AEFI 2001*

info ⇒	clinic*	parent	gen. pract.	hospital	other	unknown	event ↓	total
local reaction	31	48	4	3	-	1	-	91
general illness minor	101	265	31	2	1	5	-	446
major	12	34	14	-	2	4	-	74
persistent screaming	10	36	-	-	-	-	1	49
skin symptoms	18	38	3	2	1	2	-	73
discoloured legs	13	144	13	2	1	-	-	175
faints	21	197	55	3	5	4	-	293
fits	9	54	41	2	3	8	2	121
anaphylactic shock	-	-	-	-	-	-	-	0
encephalopathy/-itis	-	-	1	-	1	-	-	2
death	1	-	2	-	-	-	3	7
total	216	816	164	14	14	23	2	1331

* child health , school health and refugee clinic

This percentage is higher than in 2000, 1999 and 1998 (66% , 63% and 62%). Parents were the sole informer in 52 cases (21, 40 and 41 in 1998, 1999 and 2000). Hospital specialists supplied information in 16% of the reports, a little less than in 2000 (18% in 2000 and 19% and 15% in 1999 and 1998), with a small increase in actual numbers (214 vs 207 in 2000). The level of medical intervention may also illustrate the impact of adverse events. In 20% (270) of reported events no professional medical help was sought or was not reported or

recorded by us and 13% of the parents (171) administered paracetamol suppositories, diazepam by rectiole or some skin ointment for instance (in 2000 22% and 12%, respectively). 63% of the parents contacted the clinic or GP, called the ambulance or went to hospital, with in 11 % admittance. In 1997, 1998, 1999 and 2000 these latter percentages were 52%, 60%, 64% and 66% with 11%, 10 %, 12% and 13% for admittance respectively. In table 9 intervention is ordered according to highest level used.

Table 9. Medical intervention and events of reported AEFI in 2001

event↓	intervention⇒	?	none ^a	supp ^b	clinic ^c	gp tel ^d	gp visit ^e	ambu lance ^f	out-patient	emerg ency	hospital stay	other ^g	post mortem	total
local reaction		13	9	8	25	6	22	-	4	-	-	3	-	90
general illness	minor	60	57	67	49	45	91	-	23	9	19	27	-	447
	major	8	1	8	1	9	17	-	6	2	21	1	-	74
persistent screaming		6	6	22	1	5	5	-	1	1	-	2	-	49
skin symptoms		7	2	3	8	5	25	-	6	3	3	11	-	73
discoloured legs		16	21	35	23	19	38	2	7	6	8	-	-	175
faints		12	42	24	25	36	72	9	12	12	47	2	-	293
fits		2	7	4	5	10	21	4	8	10	47	3	-	121
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		-	-	-	-	-	-	-	-	-	2	-	-	2
death		-	1	-	-	-	-	-	-	-	1	-	5	7
total 2001		124	146	171	137	135	291	15	67	43	148	49	5	1331

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

6.7 Sex Distribution

Over de years more boys have been reported than girls. Gradually this has been “normalised”. In 1994 en before reports concerned boys in 60% of cases, with a gradual decrease from 1995

Table 10. Events and sex of reported AEFI in 1998 - 2001

event ↓	sex⇒	m	f	m%	1998 total	m	f	m%	1999 total	m	f	m%	2000 total	m	f	m%	2001 total
local reaction		33	31	52	69	44	42	51	89	34	39	47	75	41	46	47	90
general illness	minor	209	185	53	405	201	159	56	373	205	153	57	366	241	194	55	447
	major	49	36	58	85	58	53	52	111	63	42	60	106	44	31	59	74
persistent screaming		19	10	66	29	19	14	58	34	21	18	54	39	28	21	57	49
skin symptoms		40	29	58	75	50	34	60	85	36	35	51	75	39	34	53	73
discoloured legs		69	55	56	125	70	58	55	130	65	60	52	126	73	102	42	175
faints	collapse	80	77	51	158	119	102	54	221	124	97	56	221	128	140	48	268
	BHS	2	2	50	4	-	5	0	5	3	2	60	5	2	3	40	5
	fainting	6	5	55	12	9	8	5	18	4	8	33	13	8	11	42	20
fits	convulsions	34	31	52	65	37	38	49	77	27	35	44	63	27	28	49	56
	epilepsy	1	2	33	3	1	2	33	3	1	6	14	7	2	8	20	10
	atypical attacks	37	28	57	65	23	20	53	43	25	17	60	42	34	20	63	55
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis		-	-	-	-	-	1	0	1	1	-	100	1	1	1	50	2
death		2	3	40	5	6	1	86	7	2	1	67	3	3	4	43	7
total		581	494	54	1100	637	537	54	1197	611	513	54	1142	671	642	51	1331

to 1998 with then stabilisation to 54% for 1998, 1999 and 2000. For 2001 reports concerned in 51% of cases boys consistent with the composition of the cohorts. (table 10).

Distribution over the different events ranged from 42% boys for discoloured legs to 63% boys with atypical attacks, with events with less than 40 reports excluded. Compared to the reports in the last five years the sex distribution is compatible with two exeptions for collapse en discoloured legs attributing completely to the statistically significant decrease in reported boys for the totals of 2001. See Figure 5.

For 18 children their sexe is not known. Under unknown are several cluster reports of minor illness, local reactions and some unsubstantiated rumours. See for specifics on the events and subdivision, the respective categories under paragraph 6.9.

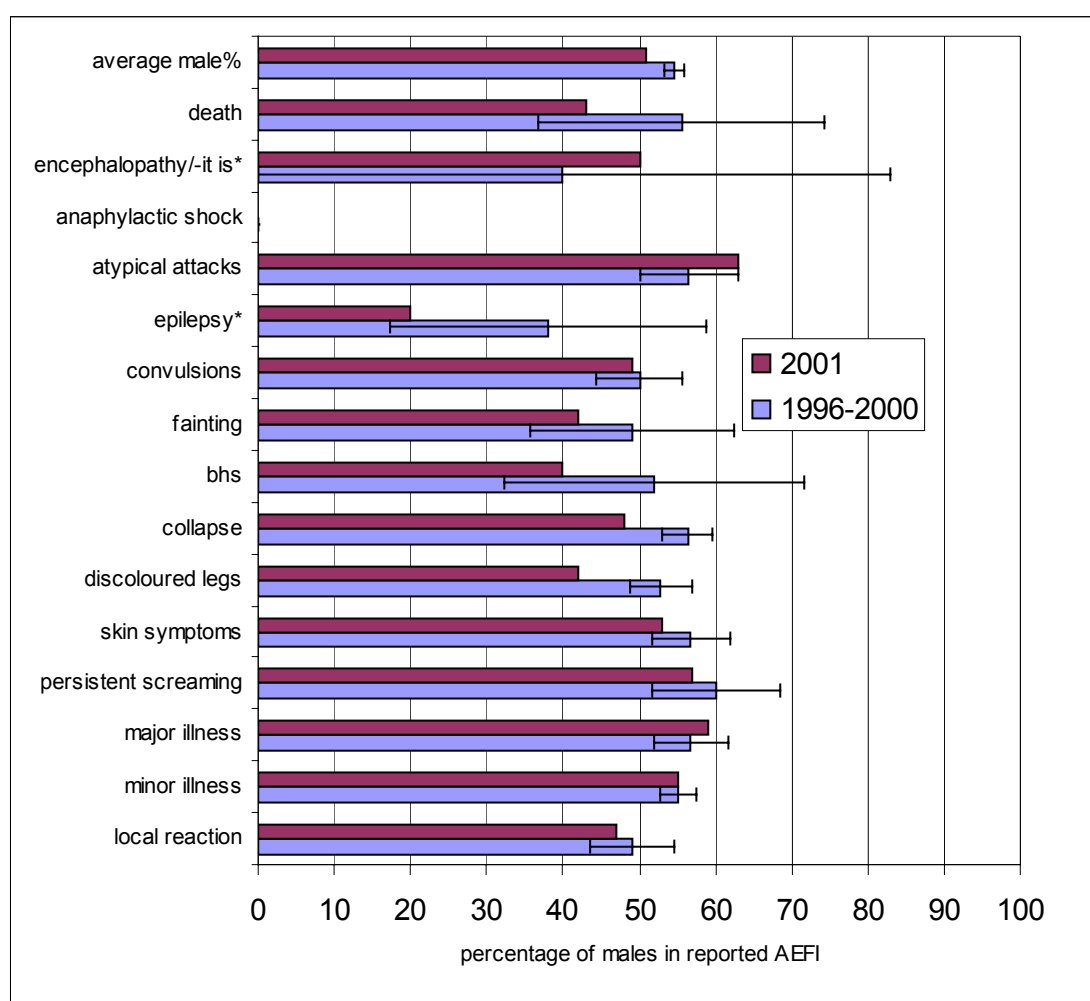


Figure 5. Events and sex ratio in reported AEFI in 2001 compared to 1996-2000 with confidence intervals (proportional with exact distribution for *)

6.8 Causal Relation

Adverse reactions are events with (likelihood of) causality assessed as certain, probable or possible. In 2001, 82% of reports were considered adverse reactions, a little higher than in 2000 (79%). For 1999, 1998 and 1997 these percentages were 84%, 80% and 80% with exclusion of the non-classifiable events. The other events were considered coincidental events with improbable or absent causal relation with the vaccinations. 17 Notifications were not classifiable (1.3%).

Table 11. Causality and events of reported AEFI in 2001

event ↓	causality ⇒	certain	probable	possible	improbable	non classifiable	total	(% AR)*
local reaction		51	26	12	1	-	90	(99)
general illness	minor	-	179	137	119	12	447	(73)
	major	-	14	19	31	-	74	(58)
persistent screaming		-	41	8	-	-	49	(100)
skin symptoms		-	11	34	27	1	73	(63)
discoloured legs		-	158	12	5	-	175	(97)
faints	collapse	-	245	11	12	-	268	(96)
	BHS	-	4	1	-	-	5	(100)
	fainting	-	15	4	1	-	20	(95)
fits	convulsions	-	13	32	10	1	56	(82)
	epilepsy	-	-	-	10	-	10	(0)
	atypical attacks	-	14	29	10	2	55	(81)
anaphylactic shock		-	-	-	-	-	-	-
encephalopathy/-itis		-	-	1	1	-	2	(50)
death		-	-	-	6	1	7	(0)
total		51	720	310	233	17	1331	(82)

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

There are great differences in causality between the different event categories, but over the years very consistent. See for description and more detail the specific paragraphs under 6.9 and discussion in chapter 7.

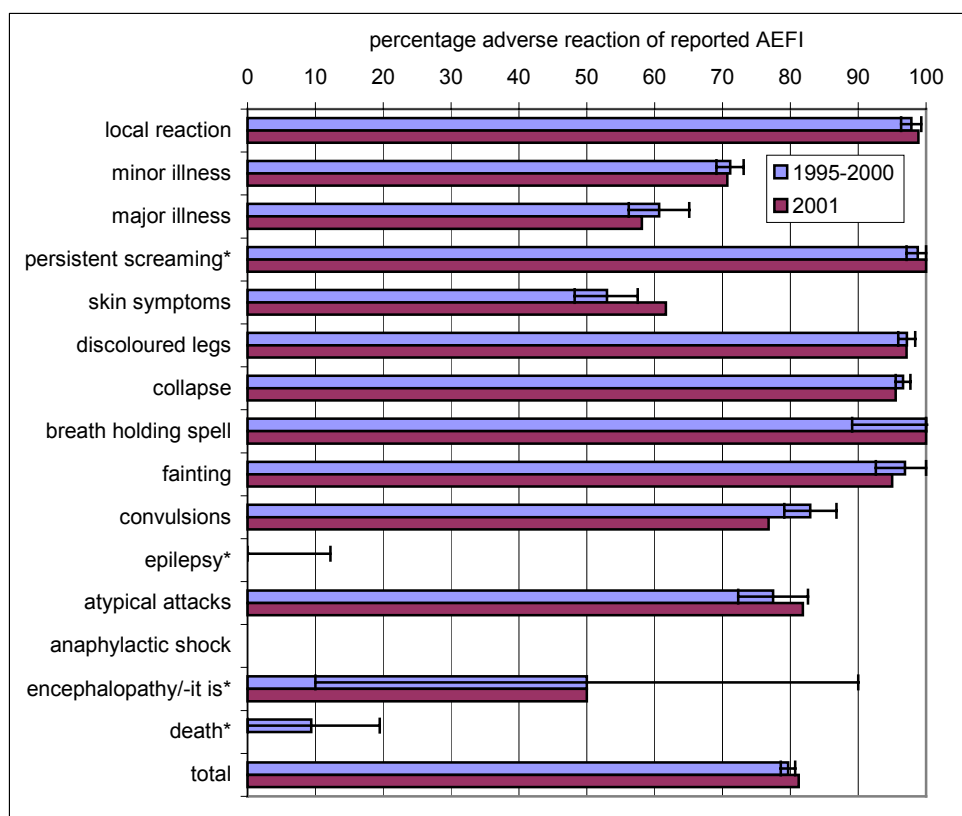


Figure 6 Causality and events of reported AEFI in 2001 compared to 1995-2000 (with 95% confidence intervals, proportional with exact approximation)*

For MMR vaccination 53% of the 197 reported adverse events were considered an adverse reaction in 2001. This was lower than in 2000 with 57% and 1999 (69%) and comparable with 1998 and 1997 (50% and 53%). For DTP, DPTP and Hib vaccinations this percentage was 87, equal to 2000. For 1997, 1998 and 1999 this was 80%, 88% and 85%, respectively.

6.9 Categories of Adverse Events

Classification into disease groups or event categories is done after full assessment of the reported event. Some disease groups stay “empty” because no events were reported in 2001.

6.9.1 Local reactions

In 2001, 90 predominantly local reactions were reported in approximately equal frequencies after DPTP/Hib or DTP vaccinations (table 12). All but one reported local events were considered reactions, i.e. certainly, probably or possibly causally related with the vaccination. (See table 11).

Table 12. Local reactions and vaccines of reported AEFI in 2001

vaccine⇒ event↓	dtp/hib1	dtp/hib2	dtp/hib3	dtp/hib4	dtp/hib?	dtp5	dtp6/mmr2	other	total 2001	2000	1999	1998	1997	1996
moderate/ pronounced	10	1	2	4 ^a	2 ^b	5 ^c	9 ^d	1	34(5)	36	39	38	36	27
Abcess ^e	3	3	2	3 ^f	-	-	1	1 ^g	13(13)	9	11	9	-	4
erysipelas/ cellulitis/ulcus ^e	1 ^h	-	-	-	-	2 ^k	-	-	3(3)	nr	nr	nr	nr	nr
atypical reaction	3	1	5	6 ^m	-	3	2	2	22(1)	25	32	22	13	15
haematoma	1	-	2	1	-	1	-	1 ⁿ	6(1)	nr	nr	nr	nr	nr
nodule	1	-	1	3 ^p	-	-	1 ^q	-	6(2)	nr	nr	nr	nr	nr
avoidance	-	-	-	6 ^r	-	-	-	-	6(0)	5	7	nr	nr	nr
total (major)	19 (4)	5 (3)	12 (2)	22 (6)	2 (0)	11 (3)	13 (5)	5 (2)	90(25)	75(21)	89(22)	69(15)	49(8)	46(11)

- a once dtp only and once major reaction
b twice clusterreport, once about dtp only
c twice following dtp+aK and once swollen arm, considered major reaction after second dtp catch up dose in refugee
d twice dtp only catch up doses; once swollen arm, considered major reaction after catch up dose dtp2 and twice major local reaction
e all considered major reactions
f once following dtp+hib4 and mmr with 1 month prior bcg in affected arm
g bcg
h once ulceration with pigmented scar
k once following dtp+aK
m once dtp only, once after first catch up dose dtp+hib and once major reaction after dtp2 and
n major reaction following influenza vaccine
p once major reaction
q once major reaction
r once dtp only

The majority of the reported local reactions (65) were mild or moderate common inflammation (29) with in 22 cases atypical symptoms, like some kind of local rash or discoloration (10), possible infection (1), (de)pigmentation (1), haematoma/fibrosis and/or dimpling (2), only swelling or itch (2) or combination of atypical symptoms (6). In six children signs of inflammation were mild or absent but there was marked reduction in use of the limb. This is booked separately as “avoidance behaviour”. The exact site of local reactions when more than one vaccine was given simultaneously, was hardly ever reported in detail, with in nine reports allocation of symptoms to a specific site or vaccine, twice DTP, twice Hib, three times aK, once right and once left with three times definitely both sided. Of the 25 children with so called major local reactions, six had extensive common inflammation once with atypical presentation, one a haematoma and two fibrosis/granuloma or nodule. Of the 13 abscesses two were drained surgically and the others drained spontaneously. To our information no cultures were taken. All abscesses were one-sided, five times DPTP site, once at the Hib site and twice (possibly) BCG. Five times the site was not specified. No faulty procedures were revealed. Three children had possible superficial infection at the injection site.

6.9.2 Systemic symptoms

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

minor general illness

In 447 children the complaints were considered minor illness in 2001. After the step up in 1998, considered mainly due to the stronger pertussis component in use, the reporting rates for minor illness have not been significantly different taking into account the larger birth cohort with an increase in the number of vaccinated children. In 2001 27% of reports were judged to have improbable causal relation with the vaccination, a little less than in 2000 (33% and in the four previous years 26-28%). See also table 11 and figure 6.

Of all reports 77% concerned the scheduled DTP/Hib vaccinations, most frequently events following the first DTP/Hib, with the relative share more or less stable over the last four years (table 13). For comparison the numbers of 1994-2000 are included.

Table 13. Minor illness and vaccines of reported AEFI in 1994-2001

scheduled vaccine ↓	1994	1995	1996	1997	1998	1999	2000	2001
dtp/hib1	104	102	85	100	117	102	120	158 ^a
dtp/hib2	53	54	47	53	81	75	53	65 ^b
dtp/hib3	37	46	34	42	60	58	45	56 ^c
dtp/hib4	13	27	32	23	54	60	55	63 ^d
dtp/hib?	nr	3	1	2	6	5	1	1
dtp/hib/mmr1	nr	2	3	1	-	2	2	3
mmr0 or mmr1	20	31	32	22	62	55	54	63 ^e
dtp5	3	6	9	3	11	7	13	16 ^f
dtp6/mmr2	5	9	1	7	12	8	23	15 ^g
other	7	-	-	1	2	1	-	7 ^h
total	242	280	244	254	405	373	366	447

^a once dtp only, twice hib only

^b three times dtp only and once hib only

^c twice dtp only, twice hib only and once dtp+hib with simultaneous synagis

^d three times dtp only, once hib only and once dtp only

^e three times mmr0 before first birthday

^f once dtp+hib three times dtp with aP and once dtp with mmr

^g twice mmr only and twice dtp only

^h once menC, once menC and pneumococcal vaccine, once hepB and once hepB and hepA vaccine, once tetanus
once influenza and once dtp(ertussis) and opv in foreign country

Only very few times it was possible to make a definite diagnosis, mostly working diagnoses were used. These are listed in table 14. Fever was the most frequent (working) diagnosis, 87, once only sub-febrile temperature (37.5-38.5°C). In all but 16 cases the fever was considered possibly causally related with one non-classifiable report. Fever was also the most frequent symptom in the other (working) diagnoses (328 times). Pallor and/or cyanosis was the second most frequent main symptom, 77 times of which 55 after the first vaccinations, all but two judged to be causally related. Another 35 times pallor/cyanosis was an accompanying symptom. Crying was the main feature in 51 cases predominantly following the first vaccinations, 37 times vehemently and seven times prolonged and seven times unusually pitched; in three cases the crying had other causes. There often was pronounced crying in the other events also (65) or groaning (13). Irritability was sometimes the (working) diagnosis (5), as were chills (14) and (sleeping) jerks or myoclonics (20), with or without fever, as often as main working diagnosis as in accompanying symptoms. One child had a bulging fontanel without pronounced other symptoms. Apathy or sleepiness was the main feature in 13 cases and gastric-intestinal complaints 19 times. Respiratory tract symptoms like common cold,

tonsillitis, pseudocroup, pneumonia, otitis, asthma, bronchitis etceteras, were frequently diagnosed (33). There were two children with red urine (myoglobuliuria?). Of the 46 children with (possible) rash illness 21 were considered to be “vaccinitis” following MMR and of the other 25 all but three were judged to be coincidental events. See for further symptoms and causality table 14. Of the reported AEFI 76 concerned MMR vaccine with in 37 cases a possible causal relation, of which ten times attributed to simultaneous DTP or DTP/Hib.

Table 14. Main (working) diagnosis or symptom in category of minor illness of reported AEFI in 2001 (with number of adverse reactions)

symptom or diagnosis	2000 (AR*)	2001 (AR*)	symptom or diagnosis	2000 (AR*)	2001 (AR*)
fever	71 (56)	87 (70)	pallor and/or cyanosis	52 (52)	77 ^a (75 ^a)
low temperature	1 (1)	5 (5)	jaundice.	- -	1 (-)
crying	42 (38)	51 (48)	rash (illness)	22 (2)	25 (3)
groaning	1 (1)	1 (1)	vaccinitis	17 (17)	21 (21)
irritability	5 (2)	5 (3)	parotitis	5 (2)	2 (2)
meningismus	- -	3 (1)	swelling face/hands/feet?	5 (4)	6 (4)
myoclonics	21 (21)	20 (18)	lymphadenopathy	4 (2)	3 (-)
chills	10 (10)	14 (12)	arthralgia/arthritis/coxitis/limping/ falling/disbalance	3 (1)	6 (3)
bulging fontanel	- -	1 (1)	allergy/atopy	2 (-)	1 (-)
listlessness	4 (2)	3 (1)	feeding problems	4 (1)	8 (4)
drowsiness	4 (4)	4 (3)	vomiting	4 (1)	6 (4)
prolonged/deep sleep	4 (3)	9 (9)	stomatitis	1 (-)	1 (-)
behavioural problem/-illness	10 (6)	13 (6)	gastro-enteritis	11 (3)	13 (1)
sleeping problems	5 (-)	2 (1)	myoglobinuria?	1 (1)	2 (2)
apnoea	1 (-)	- (-)	epididymitis/urinary tract infection/hematuria	2 (-)	1 (-)
asthma (attack)/cara	4 (-)	7 (-)	epistaxis	1 (-)	1 (-)
airway infection	10 (-)	9 (-)	headache/migraine	- -	2 (1)
cough	6 (2)	4 (1)	turning eyes	1 (1)	1 (1)
dyspnea/wheezing	6 (-)	4 (3)	nystagmus/abducens paralysis	1 (-)	2 (-)
pseudocroup	1 (-)	2 (-)	hypertonia	1 (1)	1 (1)
tonsillitis/cold	1 (-)	3 (-)	lying still/frozen	8 (8)	9 (9)
otitis	6 (-)	2 (-)	transient episode undefinable	- -	3 (1)
infectious disease	3 (-)	2 (-)	not specified	5 (-)	4 (1)
			total minor events	366 (241)	447 (316)

* adverse reactions

^a twice so called flashlightphenomenon with alternating pallor and flush

Three times the event was not classifiable. Thus in 36% of the reports of minor general illness following MMR the event was considered adverse reaction to MMR. For the other vaccine combinations this was the case in 70%, with three events not classifiable.

major general illness

In 2001, 74 reports were classified as major general illness, compared to 106 in 2000 and 85 in 1998 and 111 in 1999 (table 15). One must bear in mind that the deviding line between minor and major general illness is arbitrary. To some extent this leads to chance fluctuations within this illness category. If minor and major general illness are taken together then there is no significant difference over the years since the step up in 1998 is the larger number of vaccinated children is taken into account. Compared to 2000 there were less reports following the first vaccinations and also fewer reports following MMR1. The distribution is more even

over the scheduled vaccines than in the minor illness group. For causality see table 16. Overall, 43 events were considered adverse reactions (58%) equal to 2000. On average since 1995 reported major illness had causality inferred in 60% (range 52%-70%). See figure 6. In the 30 AEFI considered to be chance occurrences the time interval was not plausible and/or other causes were established. 23 Reports concerned MMR with in 12 cases (52%) assessed causality (40% in 2000 and 43% in 1999). For the other vaccines or combinations 32 (60%) reported events were considered to be possible adverse reactions, compared to 66% in 2000 and 75% in 1998 and 1999. See also table 16.

Table 15. Major illness and vaccines of reported AEFI in 2001

diagnosis↓	vaccine→	dtp/hib1	dtp/hib2	dtp/hib3	dtp/hib4	dtp/hib/mmr	mmr1	dtp6/mmr2	other	total
high fever		6	4 ^a	8 ^a	15 ^a	1	4	-	-	38
irritability		1	-	-	-	-	-	-	-	1
arthritis/osteomyelitis		-	-	-	-	-	1	-	1 ^b	2
pancreatitis		-	-	-	-	1	-	-	1 ^c	1
myocarditis		-	-	-	-	-	1	-	-	1
pneumonia/ bronchiolitis		1	-	-	1	-	-	-	-	2
rash illness		-	-	1	-	-	-	-	-	1
vaccinitis		-	-	-	-	-	4	-	-	4
meningitis/septicaemia		-	-	1	1	-	-	-	-	2
pyelonephritis		-	-	1	-	-	-	-	-	1
orchitis/epididymitis		-	-	-	-	-	-	1 ^d	-	1
nephrotic syndrome		-	1	-	-	-	-	-	-	1
ITP		-	-	-	-	-	2	-	-	2
haemolytic anaemia		-	-	-	-	-	1	-	-	1
diabetes mellitus		-	-	-	1	-	1	-	-	2
metabolic disease (derangement)		1	-	-	-	-	-	-	-	1
pervasive/behavioural disorder		-	-	-	-	-	4	-	-	4
retardation		1 ^a	-	1	-	-	1	-	-	3
whooping cough		-	1	-	-	-	-	-	-	1
infection/infectious disease		-	-	-	1	-	1	-	-	2
shaken baby-syndrome		1	-	1	-	-	-	-	-	2
total		11	6	13	19	2	20	1	2	74

^a once dtp only

^b bcg

^c typhoid vaccine (typhim Vi)

^d once mmr only

Very high fever ($\geq 40.5^{\circ}\text{C}$) was the working diagnosis in 36 cases and in another two prolonged high fever. In all but five cases causality was inferred. In the other events in this category very high fever was present in six cases, all in the one-year-old children, and except the three cases of vaccinitis following MMR1 considered coincidental. In other event categories there was very high fever in another 21 cases, mainly in febrile convulsions and atypical attacks. These are not listed separately under this major illness category.

Table 16. Major illness and causal relation of reported AEFI in 2001

diagnosis↓	causality⇒	certain	probable	possible	improbable	unclassifiable	total
high fever		-	14	19	5	-	38
irritability		-	-	1	-	-	1
arthritis/osteomyelitis		-	-	1	1	-	2
pancreatitis		-	-	-	2	-	2
myocarditis		-	-	-	1	-	1
pneumonia/ bronchiolitis		-	-	-	2	-	2
rash illness		-	-	-	1	-	1
vaccinitis		-	-	4	-	-	4
meningitis/septicaemia		-	-	-	2	-	2
pyelonephritis		-	-	-	1	-	1
orchitis/epididymitis		-	-	-	1	-	1
nephrotic syndrome		-	-	-	1	-	1
ITP		-	-	2	-	-	2
haemolytic anaemia		-	-	1	-	-	1
diabetes mellitus		-	-	-	2	-	2
metabolic disease (derangement)		-	-	1	-	-	1
pervasive/behavioural disorder		-	-	-	4	-	4
retardation		-	-	-	3	-	3
whooping cough		-	-	-	1	-	1
infection/infectious disease		-	-	-	2	-	2
shaken baby-sy/intracranial haematoma		-	-	-	2	-	2
total		-	14	29	31	-	74

ITP was reported twice following MMR1 with possible causal relation in both cases. One of these was a late report at the time of the scheduled revaccination at nine years of age. One child with suspected metabolic/hereditary disorder had a period of hyperammoniaemia after the the first vaccination with DPTP/Hib, administered in hospital because of suspected metabolic disorder in an older sibling. In one child with arthritis following MMR1 causality was inferred, also in a child with extreme irritability following the first vaccinations; in both cases other causes were as well plausible. All other cases have been assessed very carefully but in none inference of causal relation with the vaccination appeared warranted because of time interval and/or other established causes.

Two cases of shaken baby syndrome were diagnosed. One child with vehement crying in the night after the first vaccinations and sleepiness, both common symptoms after the vaccinations, appeared to have dated subdural haemorrhages and retinal bleeding. In the other child the parent reported the event both for advice on subsequent vaccinations and assessment of involvement of the vaccinations in this case of established shaken baby syndrome for which all other explanations than trauma had been ruled out. In both cases causality has been judged to be unlikely and absent, respectively.

6.9.3 Persistent Screaming

In 2001, 49 children with persistent screaming were reported (in 1994-2000 respectively 37, 22, 16, 26, 29, 34 and 39). Four children with possible persistent screaming are not included but only listed under discoloured legs as vehement crying seems to be part of the discoloured leg syndrome. Two children, with both very high fever and persistent screaming are included in either category because of the distinct presentation of the crying episode. The reported persistent screaming seems age/dose dependent, as has been noticed in former years (see

table 6). Local symptoms were pronounced in 24 cases, of which six mainly had (presumed) pain at the injection site and/or avoidance of movement of the legs (1). Some of the children had both sided local reactions. Additional symptoms were restlessness, feeding difficulty, and pallor. Parents were usually desperate and ten contacted the family physician and two went to the hospital, with no subsequent admissions. We did not record the degree of intervention in six cases, however (table 9). In all cases the event was considered to be causally related with the vaccinations (table 11).

6.9.4 General skin manifestations/phenomenon

In 2001 skin symptoms were the main or only feature in 73 reports (74, 75, 85 and 75 in 1997, 1998, 1999 and 2000). Discoloured legs are not included but are categorised separately. The numbers and the distribution over the different vaccine doses is rather similar to prior years, with reported events most frequently following the first two DTP/Hib vaccinations and the first MMR. See table 17.

Table 17. *Skin symptoms and vaccines of reported AEFI in 2001*

vaccine⇒ symptoms↓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	mmr1	dp5	dtp6/mmr2	other	total
angio-oedema/swelling	1	-	1	-	-	-	-	1 ^a	3
exanthema	6	5	-	1	11	1	2 ^c	-	26
(circumscribed) erythema	2	-	-	1 ^d	1	-	-	-	4
erythema nodosum	-	-	-	-	-	-	1	-	1
blister/burn	1	-	1	-	-	-	-	-	2
urticaria	2	1	2	6 ^e	4	2	2	-	19
eczema (increase)	4	4 ^f	1 ^f	1	-	1	-	-	11
petechiae	1 ^f	1	-	-	-	-	1	-	3
diaper rash	-	-	-	1	-	-	-	-	1
infantile acne/folliculitis	1	-	-	1	-	-	-	-	2
yellow discoloration	1	-	-	-	-	-	-	-	1
total	19	11	5	11	16	4	6	1	73

^a influenza

^c once dtp only

^d once hib only

^e once dtp/mmr and once dtp only and twice hib only

^f once dtp only

One child had urticarial rash with angioedema within 5 minutes after the second catch-up DTP with MMR1 simultaneously. She was hospitalised but on admission there were no symptoms anymore.

All other reported events were considered minor. Exanthema, urticaria and (increased) eczema were the most frequent symptoms, amounting to 77%. Three times there was noted vasomotor swelling/angio-oedema without rash and four times with urticarial rash. There were three children with petechial rash on upper body and/or face. Children with petechiae on the legs only are categorised under discoloured legs.

17 Cases concerned MMR1 (once simultaneously with DTP vaccination) with 13 times (possible) causal relation, once attributable to either vaccine. In four out of the five times MMR was combined with DTP there was a possible causal relation in which the symptoms could be caused by either vaccine. In the fifth case the event could not be classified because

of missing information. This resulted in possible causal relation with MMR in 77% with rashes in the second week after the vaccination (without systemic symptoms) or on the day of vaccination when causal relation could not be ruled out. The other events were not considered causally related with the vaccination, because of inconceivable time interval and/or other cause. For the other vaccines or combinations, possible causal relation was assessed in 32 out of 56 events (57%), with in the remaining events other causes assumed and/or non-plausible time interval. See table 18.

Table 18. Skin symptoms and causal relation of reported AEFI in 2001

causality⇒ symptom⇓	certain	probable	possible	improbable	unclassifiable	total
angio-oedema/swelling	-	1	1	1	-	3
exanthema	-	5	10	11	-	26
(circumscribed) erythema	-	-	3	1	-	4
erythema nodosum	-	-	-	-	1	1
blister/burn	-	-	-	2	-	2
urticaria	-	2	12	5	-	19
eczema (increase)	-	-	6	5	-	11
petechiae	-	1	1	1	-	3
diaper rash	-	1	-	1	-	2
infantile acne/folliculitis	-	-	1	1	-	2
yellow discoloration	-	1	-	-	-	1
total	-	11	34	27	1	73

6.9.5 Discoloured legs

Starting from 1995, discoloured legs are in a separate category, subdivided in blue, red or purple legs with diffuse or patchy discoloration, with or without petechial rash. Leg petechiae without noted discoloration are also grouped in this category.

Table 19. Discoloured legs and vaccines of reported AEFI in 2001

vaccine⇒ symptoms⇓	dtp/hib1	dtp/hib2	dtp/hib3	dtp/hib4	dtp5	petechiae	total 2001	2000	1999	1998	1997	1996	1995
blue legs	20	7	3	1	-	(1)	31	23	17	25	23	18	21
red legs	31	17	11 ^a	3 ^b	1 ^c	(8)	63	46	55	56	38	41	47
purple legs	23	23	8	2	-	(7)	56	47	30	30	23	27	19
petechiae only	5	11	6	-	-	22	22	9	28	14	11	13	6
swollen limb	1 ^d	1 ^e	-	-	1 ^f	-	3	nr	nr	nr	nr	nr	nr
total	80	59	28	6	2	22 (38)	175	126	130	125	95	99	93

^a once hib only

^b once dtp only

^c once dtp and mmr and "red arm"

^{d,e,f} leg, leg, arm respectively

In 2001 175 reports were received, a sharp increase compared to previous years (126 reports in 2000; table 19). Of these 31 were blue legs (26 double-sided), 63 red legs (45 double-sided) and 56 purple legs (49 double-sided). Of the 30 cases with one-sided discoloration 10 concerned the DTP leg and 7 probably the Hib leg but in 13 cases this could not be decided. In total, 38 children had petechiae, including 22 reports without noted prior discoloration of

the legs (26 times both sided). Leg petechiae with or without prior discoloration was reported 31, 30, 33, 28 and 31 times in 1996, 1997, 1998, 1999 and 2000, respectively.

About 24% (42) of the children had also fever, none $\geq 40.5^{\circ}\text{C}$ and an additional 37 had lowgrade fever (<38.5 and $\geq 37.5^{\circ}\text{C}$). Over 76% of the children exhibited fierce crying of whom three for three or more hours and another three cried over extended time, not exactly defined (none of these has been categorised under persistent screaming). Injection site reactions, if any were not pronounced, but 36 times severe pain (four times extreme) was noted/presumed, several times without other signs of inflammation. Nine children had also collapse reaction. These compound reports are grouped under collapse also. 15 Children were reported with recurrent discoloured legs after a subsequent vaccination (once a triple discoloured leg report). Distribution over the different vaccine doses remained most frequent after the first DPTP/Hib vaccinations (46%) and decreasing in number with dose number and age, a familiar pattern over the years. There has been an increase in actual numbers of reported discoloured legs however. Causal relation with the vaccines was inferred in all but five cases. See table 11 and figure 6. Further details of this specific adverse event will be published in a separate RIVM report (descriptive epidemiology and follow up of discoloured leg syndrome following childhood vaccinations, in preparation).

6.9.6 Faints

In this event category collapse (hypotonic-hyporesponsive episode, HHE), syncope (fainting) and breath holding spells (BHS) are listed (table 20).

Table 20. *Faints and vaccines of reported AEFI in 2001*

vaccine→ event↓	dptp/hib1	dptp/hib2	dptp/hib3	dptp/hib4	dtp5	dtp6/mmr2	menc	total 2001	2000	1999	1998	1997	1996	1995
collapse	173 ^a	59 ^b	29	7 ^a	-	-	-	268	221	221	158	145	120	137
bhs	2	2	1	-	-	-	-	5	5	5	4	4	7	2
fainting	-	-	-	-	7	12 ^c	1	20	13	18	12	6	7	8
total	175	61	30	7	7	12	1	293	239	244	174	155	134	147

^a once dtp only
^b twice dtp only
^c twice dtp only

In 2001 there were 268 collapse cases, in increase of 21% compared to 2000. Also reported were five children with BHS and 20 times fainting in older children. The five children with breath-holding-spells turned blue, after stopping to breathe in expiration when fiercely crying, with a very short phase of diminished responsiveness and no limpness or pallor. The distribution of collapse over the different scheduled vaccines is, as we described before, in the majority of cases after the first DPTP/Hib vaccinations (over 65%) and numbers diminishing with dose number and age²⁸. See for further information under introduction, chapter 1, and discussion, chapter 7. In 2001 there were 18 children with recurrent collapse reported (versus five in 2000), some of them with rather incomplete episodes and three of the recurrences were considered not related because of the too long time interval. In another nine children with single collapse reactions the collapse was assessed as not related because of the too long time interval and/or other causes (compared to four in 2000). See also tables 10 and 11 and figures 5 and 6 for sex distribution and causality.

6.9.7 Fits

In this category (febrile) convulsions and epileptic seizures find a place. Also “atypical attacks” in case a definite diagnosis could not be made and convulsion could not be fully excluded either, are listed here. (See also paragraph 5.5)

Most reported convulsions were febrile (51 out of 66), occurring predominantly after the fourth DPTP/Hib (19) and MMR1(28) vaccinations. The reported non-febrile convulsions are very few and evenly distributed over the different doses; the atypical attacks tended to be most frequent in the first half year of life (table 21). Fits (convulsions or atypical attacks) at the younger ages were less frequently accompanied by fever than at later doses/older ages, more so in case of convulsions than in the atypical attacks. Altogether 18 children had fever of 40.5°C and over, four times in children with atypical attacks and 14 times with convulsions. See table 10 for sex distribution and table 9 for degree of intervention.

Table 21. *Fits and vaccines of reported AEFI in 2001*

event ↓	vaccine⇒	dtp/hib1	dtp/hib2	dtp/hib3	dtp/hib4	mmr1	dtp5	menC	total 2001	2000	1999	1998	1997	1996	1995
febrile convulsion	simple	-	-	2	11 ^a	12 ^b	1	-	26	29	42	39	27	24	23
	complex	-	-	-	7	14	-	-	21	26	24	17	18	8	18
	tonic	-	-	-	1	1	-	-	2	1	1	2	1	3	10
	atypical	1 ^x	-	-	-	1	-	-	2	3	4	3	6	3	7
non febrile convulsion		-	-	2	-	2	-	1 ^x	5	4	6	4	5	4	6
epilepsy		-	5	3	1	1	-	-	10	7	3	3	5	3	3
atypical attack		13	8	10	16 ^a	8	-	-	55	42	43	65	45	28	30
total		14	13	17	36	39	1	1	121	112	123	133	108	73	97

^a once dtp only and once dtp/hib and mmr

^b once mmr0

Of the 51 convulsions with fever 43 were possibly due to the fever caused by the vaccination and considered adverse reaction. Of the eight convulsions with fever not considered to be causally related there was other cause established and/or an implausible time interval with the vaccination (six following MMR1, one after DPTP/Hib1 and one after DTP5). Of the five non-febrile convulsions two were considered not causally related to the vaccination, one after MMR1 and one after DPTP/Hib3 administration. One report was not classifiable because of missing information (menC vaccine). See also table 11.

There were ten children with epilepsy reported, of which six had (possible) West syndrome and one report with as yet undefined metabolic disorder. All were considered not caused by the vaccinations with several times prior anomalies in development and/or brain disorders. In all but one case the first seizure occurred not in a fitting time window after the vaccinations, making direct influence of the vaccination in triggering the seizure improbable; the child with a first noted seizure like episode eight days after the first MMR and a few days after an upper airway infection appeared to have partial complex epilepsy with focal activity on EEG; there also is suspicion of underlying metabolic disorder. Two children with underlying epilepsy suffered their first seizure (once non febrile and once complex febrile five hours after the third DPTP/Hib and 6 days after MMR1, respectively). Causal relation of these seizures with the vaccination was considered possible, but not with the later diagnosed underlying epilepsy.

55 Reports were classified as atypical attacks, with in 43 cases possible causal relation to the vaccination. In this subcategory there were nine children with possible chills and/or myoclonics. Three children had possible breath holding spells, and ten were hypertonic and/or limp. None of the children fulfilled the case definitions for collapse or convulsion. In 2001 MMR was involved in 41 reports, in all but twice as single vaccine (once MMR0 before the first birthday).

30 Times causality was inferred with MMR and once the event was attributed to the other simultaneous vaccines. Thus there was imputed causal relation of the fits with MMR in 73% (58% in 2000, and for 1999, 1998 and 1997, 86%, 69% and 66% respectively) and for the other vaccines in 71% of reported cases (78% in 2000 and 85%, 87%, and 76% in 1999, 1998 and 1997, respectively).

6.9.8 Encephalopathy/encephalitis

In 2001 there were two reports of encephalopathy following MMR vaccination.

One was considered to be postinfectious encephalopathy (ADEM) occurring three weeks after the first MMR vaccination. The child became sleepy and somewhat limp and could not walk or crawl steady anymore. There was low grade fever since two weeks approximately. MRI showed several lesions in the brain. Gradually the child improved with full recovery within one month. It was concluded that causal relation with the vaccination was possible, although other infections may have played a role equally.

The other child developed fever within one day of the MMR1 vaccination and had a long febrile convulsion with only gradual return of consciousness in one to two days. Two and half days after the vaccination there was another prolonged convulsion with (still?) fever, after which the child was comatose for four days. There was only very gradual and partial recovery of consciousness and mental and motor disabilities persisted. It was concluded, because of the time interval, that the MMR vaccination did not play a role in this event. Etiologic diagnosis remains unclear as yet.

6.9.9 Anaphylactic shock

No cases were reported in 2001. In matter of fact, we have never received notification of anaphylactic shock with inferred causality and/or appropriate time interval in the few cases suspected anaphylactic shock was notified, since the surveillance system was installed.

6.9.10 Death

In 2001 seven children were reported, who had died after a vaccination (see table 22). These concerned three boys and four girls. See case histories below. One boy of Dutch descent died following MMR1 vaccination abroad (in a foreign country?) and later on it became apparent that MMR vaccine from a different manufacturer was administered. It was decided to include this case in the annual report all the same since we report on all notifications we receive. In another case death followed a non-RVP vaccine, i.e. MenC, but since the same rule applies here, this case is also included. In five of the seven cases autopsy was performed, however not in all instances inclusive of full toxicologic, microbiologic or metabolic work-up or with post-mortem examination of the brain. It should be stressed however that without full post mortal investigation a definite diagnosis is often not possible.

In child F and child G the autopsy is greatly missed.

Table 22. Death and vaccines of reported AEFI in 2001

child	sex	Age ^a	vaccines	time interval illness	death	symptoms/diagnosis	Causality ^b	autopsy
A	f	14m	mmr1	47d	48d	fever since one day and post mortem revealed signs of possible infection	no	yes
B	f	15m	mmr1	39d	40d	sids with fever one day before	no	yes
C ^c	f	7m	MenC ^c	-	2d	sids	no	yes
D	m	11w	dptp+hib2	possibly weeks before	0d	unknown cause of death with at autopsy severe anaemia and increased hematopoiesis	no	yes
E ^d	m	14m	mmr1 ^d	-	7d	unknown cause of death, possibly ventolin (orally) overdosage or athma	no	yes
F	f	5m	dptp+hib2	-	0d	possible sids without any postmortal investigation	nc ^e	no
G	m	14m	hib4	6d	7d	possibly derangement of familial metabolic disease following airway infection	no	no

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

^b age at vaccination

^c child vaccinated in foreign country with MMR1 (GSK)

^d child vaccinated with MenC (Baxter) not supplied by the government

^e non classifiable

The first three reports were at first not directly reported to RIVM, but came initially as part of a rumour. Substantiation was possible with the closely knitted network of child health care.

Child A, a girl of 14 months old who received the first MMR vaccination. She died unexpectedly 48 days later. She had fever (40°C) since the day before. On post mortem examination possibly parainflueza-virus infection was detected. Both lungs were colonised with gram positive bacteria possibly caused by aspiration. There was extensive oedema of the lungs and also oedema of the brain with vascular congestion. Since none of the findings could fully explain death the diagnosis has been (late) SIDS.

Child B, was a girl of 15 months old who received the first MMR vaccination. She unexpectedly died 40 days later. The day before death she had had high fever of 40.5°C. At full postmortem there was no explanation. Therefore the diagnosis was (late) SIDS.

Child C, was a girl of 7 months old who received a menC vaccination, by choice of the parents because of some local menC clusters, but outside the locally organised outbreak control activities. No symptoms The child died within 72 hours totally unexpected and was found in prone position with the face down in the covers; Post-mortem revealed aspiration and some signs of infection in the lungs and positive cultures of blood and spleen for streptococcus viridans. Findings could not explain death. Therefore SIDS was concluded.

Child D, a boy of 11 weeks received the second DPTP and Hib vaccinations. He was seen in hospital some weeks before, at which time the distended/bloated tummy was observed. No action was undertaken however. He had several minor congenial anomalies. On the day of his

second shots the mother complained about his belly ache after he had been changed to a different infant formula the day before, with constipation since. That morning he groaned several times; she massaged his tummy for relieve. The nurse consulted the physician for this. Apart from intermittant crying like having pain shoots, and the preexisting distended abdomen, examination in this dark skinned child was unremarkable. He died approximately 3 hours later. Autopsy showed that he had very low haemoglobin (Hb 0.8 mmol/L). There was extensive extramedullary haematopoiesis existing for at least 5-6 weeks. Diagnostics into haemoglobinopathies have not been performed.

Child E, a boy of 14 months old died 1 week after his first MMR vaccination. He was treated because of asthma with Ventolin syrup orally since a week. Autopsy, without post-mortem on the brain, revealed no significancies. It could mean (clinical) SIDS, but also Ventolin intoxication or asthma attack is not ruled out.

Child F, was a girl who received the second DPTP and Hib vaccinations. Later on the day she may have had some signs of common cold. That day she was found dead in the maxi-cosy while covered with a blanket. No postmortem investigation has been performed and the child has been burried in the home country of the parents. In this case no definite diagnosis could be made. On the basis of scientific literature involvement of the vaccines appears to be remote however.

Child G, is a child reported on in the annual report of 2000. He suffered after his second DPTP/Hib vaccinations from derangement of a hereditary metabolic disease of which his elder sister died. He received a third and a fourth Hib vaccination during a closely supervised and monitored hospital stay. He did not have any complaints and was discharged after a few days following his fourth Hib. The following days were uneventful until a week after the vaccination when he developed symptoms of airway infection and started vomiting. In the following day he decompensated and died of the still not definitely diagnosed metabolic disorder.

7 Discussion

The success of the vaccination programme, having brought the target diseases under control, increases the relative importance of side effects^{10,11}. This increases the demands on the safety surveillance system like wise. Mere registration and reporting of possible adverse reactions is not enough to sustain confidence in the safety of the programme^{50,51,52}. We will discuss the characteristics of the current enhanced passive surveillance system and comment on its strength and weaknesses. We will discuss how the information in the current system may play a role in the management of adverse events and in the risk-benefit communication to professionals and parents.

The Achilles' heel of passive surveillance is underreporting. Especially selective underreporting creates distortion. Therefore the representativeness of data on AEFI presented here, will be discussed.

The year under report was again given special attention, since this is the second year in which the effect of the change in schedule to an earlier start from 3, 4, 5 to 2, 3, 4 months of age could be studied. We will discuss the effect of the change in schedule on adverse events. The increase in reports in 2001 will be discussed as will other trends or signals^{35,41}. In the latter quarter of the year the first boosters of the single acellular pertussis vaccine have been administered. Since only seven reports about this aK have been received in 2001, evaluation has to wait till 2002.

Also there has been increased attention by the public and professionals with regard to the safety of vaccines. This might influence the number and the type of events reported.

We will discuss the safety of the vaccination programme in the light of the here presented results of the current enhanced passive surveillance system (and with regard to the literature) and consider future approaches.

7.1 Safety Surveillance of the RVP

Safety surveillance of the vaccination programme seems to be of increasing importance^{10,11,53,54,55}. The Dutch system has several strong points. Denominators are known, because the PEA register all administered vaccines on individual level^{40,46}. The RVP is embedded in the regular Child Health Care with its near total coverage, therefore the programme is delivered by a relatively small group of specifically trained professionals. It is good professional standard in the clinics to ask after adverse events at the next clinic visit and before administration of the next dose. The operation of a (24-h) central telephone information service for professionals at RIVM is a most important and efficient tool in obtaining notifications. It keeps a close watch on risk perception and programme adherence. Reporting in low level terms with signs and symptoms and not only diagnoses allows application of standardised case definitions and stratified analysis if necessary. Validation and supplementation of reporting data from medical records and eye witness case histories is an important aspect of the system results in homogeneous event categorisation. Because of the wide reporting criteria the system allows sensitive signal detecting of new adverse events. The system also allows trend analysis, follow up and some other systematic studies^{38,56}.

Assessing causal relation is essential in monitoring the safety of the vaccination programme^{47,54,57,58,59,60,61}. Of course, after vaccination does not mean caused by vaccination.

Comparison of RIVM with GR assessment shows remarkable consistency. Five different categories are used for causal relation for the purpose of international comparison. However, international comparison is hampered by different criteria for surveillance systems, diagnostic procedures, causality assessment and inconsistent case definitions. On top of that, different schedules and/or vaccines are used.

The Brighton Collaboration in which RIVM also participates, aims to arrive at defined standardised case definitions for specific adverse events following immunisations. Use of these case definitions is proposed for both prelicensure studies and post registration surveillance^{7,61}.

The current passive surveillance system will need to be supplemented by more active monitoring and systematic studies to test generated signals and hypotheses. The current enhanced passive surveillance however, will remain the backbone of safety surveillance. In a current EU study in several European countries, including the Netherlands, possibilities for improved safety surveillance of vaccination programmes are being explored (Eusafevac)^{62,63}. The placement of the safety surveillance system at RIVM with its expertise should guarantee high quality assessment of the safety of the RVP.

The current enhanced passive surveillance system performs satisfactorily. The strength of the system outweighs the inherent weaknesses. See for details the sub paragraphs below and paragraph 7.5.

7.1.1 Information Service, Reporting Route and Feedback

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

It makes very efficient use of resources, which may be less obvious at the level of RIVM than in the broader perspective of management of the vaccination programme as a whole.

Education of potential reporters, while essential, will not yield much gain in efficiency for the type of reports received in a passive surveillance system. One has to bear in mind that adverse events reported in passive surveillance systems are in majority severe, peculiar, unexpected and rare events, and in case of more common events, concern special circumstances or specific underlying problems. One cannot expect that health care professionals know what specific information is needed for every possible specific event, age and vaccine and keep up with all medical literature in this respect. Education which stresses the importance of reporting and explains the type of basic information necessary to keep at hand when reporting, may contribute to further efficiency gains. Reporting by mail is possible of course, but apparently reporters favour reporting by telephone also since only less

than 4% actually report in writing. Feedback to the reporters of the final AEFI assessment is important. It should be noted in the child's chart. We will in time supply standardised written assessment forms to those reporters that want them, and perhaps offer access to report forms on an interactive website if resources allow. This will have to wait till the installation of a robust database however. Follow up of children with reported adverse events is important. This will increase our knowledge about specific adverse events, risk factors and sequelae and will in turn lead to a safer programme. We will explore how this feedback from the clinics or follow up can be done routinely in a systematic and efficient order.

There is a growing public demand for more and better information, both for general questions and for child specific problems. More readily available and accessible printed general and specific information is needed, also for professionals^{64,65,66,67}.

Feedback of the summarised annual reports on the safety of the vaccination programme should be ready in a more accessible and timely manner both for professionals and public. We are working on a five year overview in Dutch in with reported AEFI in 1998-2002 which will become available in early 2004.

7.1.2 Verification and Assessment

In the monitoring of the safety of the vaccination programme, validation and supplementation of information with follow up is considered of utmost importance. A substantial part of supplementation and verification is done in the reporting telephone call. With written notifications this is much more time consuming and will have to wait until later.

Categorisation is done according to criteria for diagnosis and case definitions and for causality. For the aggregated analysis all cases have been reappraised. Discrepancy is often quite large between reported symptom/diagnosis and final diagnosis. This discrepancy is partly due to different case definitions, but also because of more detailed further (follow up) information and more specific expertise of RIVM. The value of a detailed account by the parents, especially in case of paroxysmal events, can not be overrated. Careful history taking after the first panic has subsided is of great importance^{38,60,68}. 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 30-50 years! And for paediatricians also it is a rather rare entity with other severe events more frequently encountered. One tends to mould symptoms in known diagnostic categories. But on the other hand, reported collapse reaction does not always fulfill the criteria for collapse. Often there is only pallor or only apathy or just drowsiness or excessive sleep/difficulty in awakening and symptoms do not fit the case definition. The same applies, even more so for reported convulsions.

Skin symptoms tend to cause great concern because of feared anaphylactic reactions following a next dose. Like in former years most children with skin symptoms, even if apparent/occurring in close time relationship with the vaccination, get a subsequent dose without recurrence. Severe anaphylactic reactions have not been known to happen with the vaccines of the RVP. We prefer descriptive low level terms for skin symptoms as well as for

other categories, with no reference to possible pathophysiological mechanisms, like allergic reaction, for which there seems no justification most of the time.

The use of strict case definitions assures homogeneous diagnostic groups with possibility of epidemiological studies for risk factors and sequelae. Together with follow up this may lead to founded adjustment of indications, contraindications, vaccines or schedules as well as to proper precautions when administering a next dose. For collapse reactions this kind of follow up study has shown a low rate of recurrence after further pertussis vaccinations^{38,60}. See also under specific events paragraph 7.3.

7.1.3 Reporters

The vast majority of notifications come from Child Health Clinic staff. As professional standards require asking after adverse events routinely and nearly all children attend the clinics this gives good coverage of the safety surveillance. It is expected that few severe events are missed. We try to stress that paediatricians and child neurologists should report more often in training courses. Especially (severe) events or diseases after vaccinations which they themselves hold to be (clearly) coincidental but parents may regard as vaccine associated (later on). This to not much avail apparently. We have used the NSCK (the Netherlands Paediatricians Surveillance Unit) to study two specific adverse events (i.e ITP and ataxia following MMR or any other vaccine).

It is important even if paediatricians are not the initial reporter that hospital information is made readily available when clinic staff report the event. Only then is it possible to counteract public unrest (pro-actively). This should also enhance the ability of the safety surveillance system to detect new and hitherto unknown adverse events. Reporting by paediatricians or GP's may lead to earlier notifications. It does not make contact with the Child Health Clinics unnecessary however, as the latter have valuable information on growth, development and health and of course data on the administered vaccines. Therefore we have asked clinic personnel to notify anyway, regardless of (supposed) reporting by others. This includes cases where they asked parents to report themselves or heard from the parents that they have done so. Distribution over the different reporting sources has remained stable over the years however, except for some absolute and relative increase in reporting by parents.

Events that are more easily missed are those following vaccinations without a close follow up clinic visit. This will possibly affect MMR1 vaccinations to some extent and especially the revaccination at four and nine years of age. Emphasis will be put on this in training and refresher courses. In the information leaflets for the parents it should be stated more explicitly that in case of severe or peculiar unexpected adverse events, parents should not only contact the GP but (later) also the clinic. In the leaflets of the MenC campaign in 2002 this phrase has been included with instruction to the municipal health organisation to pass on the report to RIVM. This has resulted in a high reporting rate and a very close watch on the safety of this mass vaccination campaign. The MenC campaign will be reported on separately. Active follow up as planned within the EU safevac project should throw some light on the extent of underreporting of some specific adverse events following DPTp-Hib. See also subparagraphs 7.1.6. and 7.2.1.

7.1.4 Source of Information

Information about the adverse event was retrieved from others than the initial reporter in 78% (67% in 2000). See also what is said about this under verification and assessment in sub-paragraph 7.1.2. Not only were parents more often than before reporters of AEFI but also more parents were contacted (actively or spontaneously) for further specific information than the year before, not only because of the severity but because of apprehension in parents and providers as well. Parents do call the telephone service for professionals for information about the (safety of the) programme, increasingly. Anti-vaccine-movements add substantially to public concern about possible adverse events in the Netherlands as in other countries ⁶⁹. Contacts with parents is necessary anyway since permission has to be acquired to request medical information from GP or hospital. Increasingly the reporters have insufficient information, necessary for categorising and causality assessment. Often the reporters do not have first hand information. Hospital information was received in 214 cases with a deficit of nearly 50 in which the child was seen by the specialist but we did not receive information despite repeated request en permission by the parents. In the end these cases could be assessed reliably however.

7.1.5 Regional Distribution and Reporting Rates

We have standardised the number of reports per region on rate per 1000 vaccinated infants (for the first three doses DPTP/Hib). Since the actual numbers of vaccination coverage and population in the different regions are only available up till 1999 as yet, the rates for 2000 and 2001 are based on these data. Apart from the slightly larger birth cohort (+2.5% according to CBS data) this is held to have little distorting influence. The overall reporting rate has gone up significantly in 2001. Regional reporting rates have gone up significantly as well in six of the 15 regions and in the other nine the differences in rates could be random fluctuation. There was a little more dispersion in the regional rates than in 2000. Comparing type of events and severity does not show large differences between these two groups of regions. In the six regions with the larger increase in reporting rate there were a slightly larger proportion of minor events than in the regions that did not show a significant rise. Perhaps this testifies to a some further decrease in underreporting and/or to an increase in public apprehension. See for more details under paragraph 7.2 and 7.3.

7.1.6 Passive Surveillance versus Active surveillance

Active surveillance may supplement our enhanced passive surveillance system. Periodic study of tolerability of the used vaccines is warranted, not only in case of signals or expectations of change in this respect. A planned study for the tolerability of DPTP/Hib got thwarted because the planned MenB trial was postponed and in between an accelerated schedule for DPTP/Hib vaccines was adopted. This accelerated schedule however in itself deserves specific study of overall tolerability at a younger age. In 2004 we plan to complete an active study in about 10,000 children for the four doses of DPTP/Hib started as part of an EU project, for rare and severe events (EU safevac). This study may also assess the performance of our current enhanced passive surveillance system. Passive surveillance however will remain the backbone of post marketing surveillance and the most appropriate

tool in signal detecting. For testing hypotheses generated by passive surveillance systems active follow up through monitoring or data linkage designs need to be employed. With relying on only active surveillance the safety-surveillance-system is “unmanned” for testing generated hypotheses since that will not be possible anymore within the same system. Therefore enhanced passive surveillance as well as designs for hypotheses testing are of importance and should be employed in the right order ⁷⁰.

7.2 Increase in Number of Reports

Since the large step up of 1998, the reporting rate has stabilised in 1999 and 2000. In 2001 however, there was another increase (17%) that cannot be explained by the larger birthcohort (plus 2.5%) or a larger number of administered vaccines. The capacity of the telephone service, the main route for reporting, has been very much under stress in 2000 and 2001, due to resources with subsequent inaccessibility. This may lead to “evaporation” of notifications, as has been known to happen before when the telephone service was flooded with calls in the period of the last polio epidemic when there was additional shortage of personnel because of illness and vacancies. We have received no signals that notifications have gone up in thin air in the year under report however, but some complaints have come in. Reporters know of course that notification can also be done by mail. There is no increase in reporting by mail, however. The telephone service is also used for consultation and advice and since quite a high number of reports reach us because of the need for consultation, we have to assure that the telephone service is “open”, in order not to miss a substantial part of notifications.

There is a marked increase in multiple reports: 64 compared to the 40 in 2000 (versus 26 in 1998 and 14 in 1997) accountable for 52 events of the total increase of 189 events. This may be due to increased follow up efforts of the initial notification, by both RIVM and the original reporter or parents. Minor common events that come up during follow up by RIVM are not included unless the events are explicitly reported. Uncommon and major events are always included in the numbers whichever way the events came to the attention of the surveillance system. This policy has not been changed since 1994, therefore it offers no readily acceptable explanation for the increase in reports. See for criteria the materials en methods section, paragraphs 4 and 5.

Reporting criteria have not changed either over the years, but awareness of professionals and the public has increased lately, partly because of the publicity around new/to be introduced vaccines. Recently the need for vaccinations and their safety has been questioned by certain groups ^{13,69}. Public awareness of the seriousness of the target diseases has diminished since the illnesses have been effectively prevented for many years now ^{71,37}. Consequently more value is attached to (potential) side effects. This influences the readiness to report perceived adverse reactions. Reporting criteria for adverse events following immunisation are flexible and subject to personal interpretation and circumstances. Our system registers any notification, regardless the reporting criteria, time interval or causality.

Some degree of underreporting is inevitable and for some events this may need extra specific designs, but overall the increase in numbers of reported AEFI cannot be explained by a further decrease in underreporting. There seems to be an actual increase in occurring side effects,

mainly vasomotor events like collapse, pallor en discoloured legs. This could be the result of lower age at vaccination on average than in the first years of the new schedule. See for details and discussion on the increase the subparagraphs below and the specific events in paragraph 7.3.

7.2.1 Underreporting

Reducing underreporting is of special importance in passive surveillance systems, especially of selective underreporting. Since 1994 we have put extra effort into this, as has been discussed in previous annual reports ^{32,33,34,35,37}. It has been concluded that the rise in number of reports in 1994-1997 resulted mainly from this effort, with a minor influence of the introduction of a new vaccine (Hib) from July 1993 onwards. The increase in number of reports in 1998 was held to be partly due to a further decrease in underreporting, increased apprehension or awareness, but also to an increase of real adverse reactions caused by the use of the higher potency pertussis component in the DPTP vaccine ³⁴. The reports of 1999 were difficult to interpret since the change in schedule did not apply to the full calendar year but only to the children born in 1999 (and after) which resulted in vaccination of an extra number of children ³⁵. The number of reports in 2000 were comparable to 1998, but there was some shift in the type of reported events, held to be due to the effect of the new schedule, with earlier start. The increase in number of reported AEFI in 2001 may be partly due to a decrease in underreporting in some regions with a somewhat larger proportion of minor events in the regions with the highest increase in reporting rate, but this certainly cannot explain the total increase in numbers. Especially since the increase in reported events is not evenly distributed over all event categories and over all vaccine doses. See subparagraphs below and discussion of the specific adverse events in paragraph 7.3.

7.2.2 Distribution over Vaccines and Dose

The distribution (relative frequency) of all reported AEFI over the different (doses of) vaccines is rather similar to 1994-2000 (table 5 and figure 2). This gives no indication of selective underreporting and points to very stable reporting habits. The increase in number of reports (17% more) as compared to 2000, is on account of the first three doses of DPTP/Hib. Numbers for the other vaccines are stable. This seems to point to some aspect of those specific vaccine doses.

7.2.3 Distribution over Events

The distribution of reports across event categories is also rather similar over the years (table 6 and figure 3). Within each event category over the different (doses of) vaccines. Some increase/decrease may be random fluctuations. There is no indication of systematic underreporting. The reporting rate of collapse reactions and febrile convulsions have been rather stable and close to incidence rates shown by prospective studies ^{72,73,74}. However, background rates of most events are not known, and there may be (substantial) underreporting for some. For instance, the ITP reporting rate is lower than some studies suggest ^{75,76}. This needs to be studied in an active surveillance design. Since reporting criteria include severe events regardless of assumed causal relation, perhaps all severe events, occurring in the applicable risk window for the specific event and vaccine, should be

reported. The number of reported discoloured legs has been rather stable over the years is rather stable, with perhaps a step up since the use of higher potency pertussis vaccine. However, we have no indication of the completeness of reporting of this specific event. Therefore discoloured legs are included in the active surveillance for Eusafevac. Persistent screaming shows underreporting, in view of estimates in prospective studies (that did not apply uniform case definitions). In some cases, during our assessment of the notifications of persistent screaming, verification showed that some reports did not fulfil the current case definition. In 2000 there was a significant increase in reported collapse reactions possibly because of the change in the schedule. For 2001 there was another increase in collapse reactions may be again due to a further decrease in age of vaccination. There was an increase in reported discoloured legs, persistent screaming and in the minor illness event category of pallor and crying as well. This all fits an age effect. For febrile convulsions, mainly after the fourth dose of DPTP/Hib and the first MMR there was no increase in reports. See for further information 7.2.5 and the specific events under 7.3.

7.2.4 Severity, Reporting Interval, Causality and Level of Intervention

We have checked for the different severity markers/parameters, such as major versus minor events and level of intervention. More parents contacted the clinic or phoned the GP than in previous years (272 versus 183, 168 and 94 in 2000, 1998 and 1997), and 569 were actually seen by the GP or hospital specialist (525, 472 and 348 in 2000, 1998 and 1997) with the proportion of children seeking medical attention, all levels combined (63%) rising a little compared to 2000 (62%, 58% and 54% in 2000, 1998 and 1997, with 1999 excluded because of unknown denominators). This also seems to point to increased concern if not to increased severity.

The reporting intervals, another indicator of severity or anxiety, for different doses and events have been compared. The reporting interval, did not shorten again, but was 35% within 4 weeks (before the next clinic visit), compared to 37.5% in 2000 and compared to 33.4% in 1998. The reporting interval of MMR did decrease, with reporting within 4 weeks in 47% of all cases, again a 6% increase (41% in 2000 and 34% in 1998). This may have been caused by adverse publicity about safety of the MMR vaccine. But could also be a sign that efforts to enhance the surveillance have worked out well. There was no increase in actual numbers compared to 1999 and 2000 with the proportion of reports with possible causal relation a little lower in 2001.

The increase in number of the more severe (major events and minor events with hospitalisation) is fully attributable to the increase in collapse reactions, discoloured legs and persistent screaming. The share of major events, by our definition, together with minor events with hospital admission increased from 56% and 54% in 1997 and 1998 to 58% in 2000 and 2001.

For the first three doses of DPTP/Hib, the percentage considered to be adverse reactions rose to 88% (84% in 2000) and is again mainly attributable to the increase in collapse, discoloured legs and persistent screaming, all three acknowledged adverse reactions. For the fourth dose of DPTP/Hib the percentage of adverse reactions decreased to 76% with statistically significant

greater share of coincidental events reported than in 2000 and 1998. There is no ready explanation for this. The overall percentage of assessed adverse reactions (with causality assessed as certain, probable or possible) is 82% a little higher than on average over the last six years but within range (78%-84%).

7.2.5 Accelerated Schedule

The change in schedule since the 1999 birth cohort did not affect the reporting rate in 2000. The distribution over the different vaccine doses and events was rather similar to before. The younger age at vaccination for the first three doses did not result in a shift in total numbers and reported events. Therefore, reported events appear to be more dose- than age-specific. It is known that vaccination at a younger age results in fever and local reactions than at a later age⁷⁷. Since the event categories of minor and major general illness are very heterogeneous, the numbers presented here do not yield firm conclusions. The increase in numbers in 2001 was, apart from collapse, discoloured legs, and persistent screaming, mainly due to pallor and crying in the minor illness group. This could be the effect of better adherence to the accelerated schedule with on average younger age at vaccination reflecting the less stable vasomotor system. The stable numbers for the other vaccines and doses is in line with this for these vaccinations are not affected by the new schedule. Since PEA data on vaccination do not include the exact day of vaccination we have no precise data on the timeliness of the first three doses. This warrants further investigation to test this hypothesis. A special query in the PEA database may substantiate or refute this supposition of younger age. Active follow up, as planned for the EUsafevac project may shed light on the incidence rates of some of these specific events and on the age at vaccination. See under collapse and discoloured legs below.

7.3 Specific Events

In addition to what is said in paragraph 7.1 and 7.2 on specific adverse events with respect to the increase in reported adverse events, some specific events or event categories are discussed below.

7.3.1 Collapse reaction

Reports of collapse reactions again appear to have truly increased with 21% compared to 2000. Numbers and distribution over the vaccine doses have been rather stable over the past years, with around 100 reports of collapse following the first DPTP/Hib dose (at three months of age) and approximately 25 and 15 reports after the second and third dose. Since the change in schedule the total number of reported collapse reactions has gone up with nearly 80% for the first three doses (OR 1.82, c.i. 1.49-2.23). Distribution over the different doses leveled off a little bit further, which suggests a strong dose effect and a (little less pronounced) age effect, since some increase of collapse occurred after the second dose again in 2001. The number of reported collapse reactions at three months of age, assuming the average age to be the same as earlier with the first dose, would have been about 100 instead of the actually reported 60. We have little reason to believe that this is due to reporting bias or (diminished) underreporting. Apparently, to some extent a previously received dose of DPTP/Hib vaccine protects against collapse reaction at three months of age. Cytokines/mediators/interleukins

that are part of the primary immune response but are not formed (as much) following subsequent contacts with the antigens may play a role. We will comment on this in our report on collapse reactions (in preparation).

There was also some increase in reported recurrent collapse, some with (very) incomplete episodes and three of the recurrences not believed to be due to the vaccination. This may be an indication that the accelerated schedule raises the risk on recurrence a little. We will have to look into this more systematically.

7.3.2 Discoloured legs

Numbers of discoloured legs are higher than those in previous years. The above made remarks on collapse reactions also apply here. Distribution over the different doses remained the more or less the same, with some effect of the younger age, also suggesting a stronger dose than age effect unless the average age for the second and third dose still lags behind. Lacking incidence rates of discoloured legs from prospective studies, we can only speculate. The reporting rate of the discoloured leg syndrome has been rather constant since we made it a specific category and applied case definitions, until this year, with however some levelling of the numbers for the first three doses since the new schedule applies. The numbers for the fourth dose remain low. This does not suggest selective underreporting. We will try to estimate incidence rates in the active follow up within the EUsafevac project. We will report on discoloured legs in a separate publication (in preparation), in which some follow-up data will be included ⁷⁸.

The number of compound reports with both collapse reaction and discoloured legs is stable over the years (6, 6, 7, 8, 7 and 8 in 1996, 1997, 1998, 1999, 2000 and 2001). Whether the accelerated schedule increases the risk of recurrence of the discoloured legs or not remains to be seen. Recurrence does happen, not necessarily following the next dose, but remains without sequelae.

7.3.3 Apnoea

In 2001 we have not been notified of apnoea even once. In 1999 and 2000 we had several reports of apnoeic incidents in (extremely) premature children. This is apart from the apnoea in possible BHS or as part of convulsions or collapse reactions.

Risk benefit balance of the vaccination in extremely premature children favours vaccination at an early age. Pertussis is extremely hazardous to them. Therefore the normal accelerated schedule may be applied for premature children. There is a (increasing?) tendency to vaccinate those very premature infants during hospitalisation. Since this does not prevent the event to happen we may be we should have received more notifications.

7.3.4 Convulsions and Atypical Attacks

The number of (classic) febrile convulsions following DPTP/Hib and MMR1 vaccinations were rather similar to 2000, 1999 and 1998. This is not surprising since these events occur most frequently after the fourth dose, and this dose is not affected by the change in schedule. In 2001 two febrile convulsions after the third dose of DPTP were reported, both in children 5.5 months old. This may reflect the younger age of this dose on average, with subsequent lower (background) rate of febrile convulsions. The number of reports with atypical attacks

was a little higher than in 2000 and lower than in 1998 and comparable to 1997. One has to bear in mind that this is a subcategory for non-specific paroxysmal events that do not fulfil the criteria for collapse or for convulsion. Therefore the number is (very much) dependent to completeness of information. Thus, in different years transfer to and from other event categories varies. If planning and priorities permit, we plan to look into the phenomenon of atypical attack in more detail. The stable and low number of reports of non-febrile convulsions may reflect non-causality in the first place ⁷⁴.

7.3.5 Local Reactions and Abscess

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

7.3.6 Skin Symptoms and Allergy

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

7.3.7 ITP, Gait disturbance (ataxia)

ITP numbers have remained low throughout the years. The rate of ITP after MMR1 in the literature is much higher than we get reported. The causal relation of ITP following other RVP vaccines remains speculative. An active surveillance study has been started in 2002 through the Netherlands Paediatric Surveillance Unit (NSCK) in order to gain more insight on ITP and its relation to vaccinations ^{36,76,79,80}.

Biologically, it is plausible that MMR may cause ataxia, but there are no systematic data ⁸¹. We get very few reports, maybe because of the lack of causal relation with the vaccine. In the year under report six walking difficulties have been diagnosed, but none fitted the case definition for ataxia. In two nine year old children the disturbance followed MMR2 and was more likely the result of anxiety than somatic. In the other four children, all one year olds, the difficulty in walking did not get a final diagnosis or etiologic agent. All recovered and three had possible causal relation with the MMR1 vaccination because of the time interval. Ataxia is also included in the active surveillance study through NSCK.

7.3.8 Anaphylactic shock

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

7.3.9 Encephalopathy

Encephalopathy following pertussis vaccination seems to be one of the “wrecks of once known and acknowledged truths strewn on the pathway of medicine” (citation of Barbara Tuchman). Since 1987 we have had no report of encephalopathy possibly attributable to DTP (pertussis) vaccination. All reported events had other etiology, like chromosomal or genetic disorders, like Reye syndrome, virus or mycoplasma encephalitis, metabolic diseases or intoxication (salicylate or Tramal eg). Also some vascular accidents like thrombosis with underlying clotting disorders have come to light. Lately some children with shaken baby syndrome were reported. The increased possibilities to detect metabolic diseases and chromosomal or genetic disorders have greatly contributed to diagnostics in these kind of events, and so have virological tests, PCR and last but not least MRI.

Reports of encephalitis following MMR are rare. In a few instances causal relation could not be ruled out, since no definite cause could be identified and the event occurred in the risk window for MMR (1: 500,000-1,000,000 children). In the year under report, two cases were received of encephalopathy both following MMR. One, with complete recovery, was possibly caused by MMR and the other was considered unrelated because of unfitting time interval with the vaccination.

7.3.10 Pervasive Disorders and Retardation

Press allegations about possible causal relation between MMR vaccination and autism dented the confidence of parents in the vaccination programme^{82,83}. Despite the fact that based on scientific evidence renowned (groups of) scientists have refuted these alleged associations, especially in the United Kingdom and Ireland the vaccination coverage dropped considerably^{84,85}. We have received some reports on behavioural problems in the autistic spectrum, often quite some years after the MMR vaccination. Some parents have no real suspicion but have been made insecure, others simply clutch the last straw. In none of the reported cases a causal relation was found, and in some the event preceded the vaccination.

It is to be expected that reports of events that have attracted attention in the press will increase. A passive surveillance system, even an enhanced one, is not the proper tool for a refutation of false hypotheses. Recently a few systematic studies have been published showing no causal relation of disturbances in the autistic spectrum with MMR vaccination or thiomersal containing pertussis vaccine^{86,87}.

7.3.11 Epilepsy

There has been some increase in reports on epilepsy compared to previous years, concerning very small numbers. This may reflect public apprehension. Current scientific data do not support causal relation between epilepsy and vaccinations. In the past years a number of studies have been done on the etiology of epilepsies⁷⁴. However, it may not be possible to exclude this definitely in an individual case. Vaccines may cause convulsions, mainly indirectly through fever. As for West syndrome, epidemiological evidence refutes a causal relation^{54,88}. However, the age at which it occurs coincides with the vaccination schedule.

7.3.12 Death

This year seven children were reported two not following vaccinations under the RVP. In view of the average over the years, this is in line with expectations. Systematic studies and evaluation of the Institute of Medicine have shown infant death to be unrelated to childhood vaccinations⁸⁹. In an individual case, this may not be demonstrated easily. Especially in the case of possible SIDS this poses a problem. Diagnosis of SIDS is possible only after extensive post-mortem examination has not revealed a cause of death. Therefore it is of utmost importance to insist on full post-mortem investigations and to report fully on all infant deaths following vaccinations. Even if causation is very remote, it is known that in the direct surroundings of the case there is an adverse effect on compliance to the programme, of public and professionals. The first three reports in the year under report were at first not directly reported to RIVM, but came initially as part of a rumour. Although substantiation is usually possible with the closely knitted network of child health care, it should be emphasized that death in close time relationship, i.e. for inactivated vaccines within one week to one month and for live vaccines within six weeks, should be reported in all instances, regardless of cause. Sooner or later someone will question the effect of the vaccinations even if on first sight causal relation seems to be remote. It is better to be pro-active than to have to follow up on (public) disquiet. If parents are not aware of notification, reporting anonymously is the better choice than to postpone until parents are consulted. To explain that assessment of the involvement of prior vaccination is done routinely and not only if there is suspected contribution of the vaccination in the death will satisfy most parents.

In the year under report, in none of the cases the vaccination we judged to have played a (direct or indirect) role in the events leading to death. Since no full autopsy was performed, the cause of death could not be determined in two cases. Since no full autopsy was performed, the cause of death could not be determined in two cases. Causal relation was judged to be unlikely, even without a definite cause of death. One child has been diagnosed as possible clinical SIDS and the other as (clinical) SIDS or intoxication of Ventolin syrup or asthma attack. In one of the other cases there might have been severe and life threatening underlying disorder at the time of vaccination, since very low haemoglobine levels that have been found at autopsy with no evidence of trauma. This was however not suspected by the Child Health Clinic professionals nor by the hospital at previous examination. It is unlikely however that the vaccination has played a role. On hindsight postponement of the vaccination would have relieved the vaccine from the burden of suspicion; the child would probably have died anyway.

7.4 Management of Adverse Events

The increasing relative importance of potential side effects makes careful surveillance of the safety of the vaccination programme even more important than before. Just signal detection isn't enough. See also under paragraph 7.1. Evaluation and feedback communication should complement mere registration. Signals should be followed up with more systematic studies. Information about reported adverse events should have a place within the risk communication to parents. Some side effects are unavoidable but where possible the aim should be to prevent

side effects. Adverse coincidental events are truly chance occurrences however. Sometimes postponement of vaccination might free the vaccine and the vaccination programme from allegations of causing an event or disorder that would inevitably have occurred. But deferral should be avoided as much as possible because it will delay protection of the child.

7.4.1 Prevention and Treatment Adverse Events

Adverse reactions or side effects do occur and parents should know what to expect. They need instruction about what (not) to do to alleviate symptoms. In the communication about the risk of vaccination, attention should be paid to the decrease in (awareness of the risk of) occurring target diseases. It should however also be stressed that not everything occurring after a vaccination is indeed caused by the vaccine. One of the most severe adverse events is undue, even fatal delay in recognising severe coincidental illness, because for too long the vaccine was thought to be the cause of the illness. Some education of the professionals in this respect seems warranted also. The vaccination as cause should be in the differential diagnosis, nothing less but at the same time nothing more.

Proper procedures and techniques are important in minimising adverse reactions and the proper use of paracetamol should be included in the information to parents.

7.4.2 Contraindications

Contraindications for the RVP vaccines have been abandoned more or less completely^{38,41,57,58,90}. Proper application of true contraindications should be adhered to however to prevent undue side effects. But false contraindications should be avoided on the other hand because they lead to missed opportunities to provide protection. In the year under report abandoned contraindications do not seem to have contributed much to the number of reported events. And therefore prevention of side effects will not gain much in using more strict contraindications and only result in a loss of protection.

7.4.3 Risk Communication

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

7.4.4 Causality Assessment

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

7.5 Considerations for the Safety Surveillance of the RVP

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

The tolerability of the currently used vaccines might be measured, partly in the phase II and III trials in which the registered vaccines are used in the control groups. But in case of changes in schedule or of included vaccines active tolerability monitoring should be included in comparative design (pro-actively thus)⁷⁰. This can not be left to the (different) involved manufacturers but should be part of programme surveillance.

Standardised case definitions and reporting criteria are a must.

Passive surveillance and active studies are both needed since hypothesis testing cannot ever be done within the same data (system) that generated the hypothesis.

Active surveillance to check on overall tolerability of known but more rare events following the vaccinations is also part of an EU project (EUsafevac). Gait disturbances (ataxia) and ITP after MMR1 are the studied events in active design through NSCK. These studies may shed light on ITP and gait disturbances as adverse events and on the relative performance of the current passive surveillance system.

A well performing, good quality passive safety surveillance system such as exists in the Netherlands should not be taken for granted but requires maintenance and investment. On the other hand shortcomings as overdue privacy concerns and the absence of outcome databases or common personal identifiers, that may be used for datalinkage purposes, should be addressed. Without the use of these new epidemiological designs that may expand our knowledge of adverse events may be hampered. An adequate database system is a prerequisite for this as well. The data put into the system must be of good quality nevertheless, therefore this should get a lot of attention. "Rubish in rubish out" also applies to safety surveillance.

After successful prevention of the target diseases the relative weight of adverse events increases. Parents and providers expect careful safety monitoring of the vaccinations. Anti-vaccine-movements will be more active in the future. A comprehensive surveillance system will be instrumental in refuting unfounded allegations.

Providers must be supplied with timely and adequately referenced information about any suggested association of severe adverse events and vaccination in the media or medical press. This will enable them to answer questions from the public. Clinic staff stress that convincing parents of the benefits of the vaccination programme takes more time than before and indicate that resources fail. Often parents already have information from other sources and it is not easy, if at all possible, for them to decide on its quality. The sites of anti-vaccine

movements on the Internet are much more readily accessible than the more balanced information about the merits of the programme. There is increasingly need for fact sheets per target disease and per vaccine. The possibility of adverse events in general and how to act as parents in case of should be addressed. Periodic actualisation of the RVP guideline book is also necessary but these updates will lag behind and not meet the need for timely information to inform on or refute false allegations. Lately the Minister of Health has recognised this need in a letter about the RVP to the parliament (2nd of October 2000). And the start of a project for improving public information on the vaccination programme in 2003 is a first step in meeting some of the above discussed needs.

8 Conclusions and Recommendations

In 2001 the number of reported events rose again rather unexpectedly, after stabilisation of the numbers following the step up since the introduction of the higher potency pertussis component in the DPTP vaccine in 1998. Initially the acceleration in schedule since the 1999 birth cohort has not lead to an overall increase in reports. The increase in reported collapse reactions nevertheless has continued in 2001 as has the shift in collapse and discoloured legs over doses and ages. This has lead to an overall increase in numbers of reports of 17%. The increase in pallor and crying in the reports may be an indication that the earlier start of the vaccination schedule plays a role in these events as well, as result of a better adherence to the new schedule. This warrants further investigation as does the possible rise in number of recurrent collapse reactions. This will have to be subject to further study.

Periodically the overall tolerability of vaccines used in the vaccination programme should be studied with special attention to perceptions of providers and parents. The change in schedule from birth cohort 1999 onwards to an earlier start of the programme makes direct comparison with prior studies not entirely possible anymore, however. And the change to mixed administration of DPTP-Hib, from march 2003 onwards, may compromise this even more. The EUsafevac project study may supply some information on the tolerability of the vaccine, as may the planned field trials of new vaccines (combinations).

Overall regional distribution of reports seems very satisfactory, although there seems to be substantial underreporting of some adverse events. We have included ITP and gait disturbances (ataxia) following (MMR) vaccination in one of our data linkage pilots. (EUsafevac). Detailed study of epidemiology, sequelae, follow up and risk factors should be performed about some specific adverse events, e.g. collapse, discoloured legs and atypical attacks/non-febrile convulsions in the near future. Also we will have to look into the abscess cases for risk factors.

The telephone service for reporting, consultation and advice is an efficient and important tool of the enhanced passive safety surveillance system and in the management of the RVP. Its quality should be maintained and if possible its performance studied.

The planned database system for adverse event surveillance should allow further detailed aggregated analysis of the reports and also facilitate systematic feed back to the reporters as well as data exchange with other bodies, nationally and internationally. Safety surveillance systems of the future should be prepared to study generated signals of specific rare or long-term adverse effects on short notice. Especially now that introduction in the RVP of more (novel) vaccines is expected in the forthcoming years (foreseeable) safety concerns should be included in the discussion about introducing the vaccines in the programme. Stratified introduction could be helpful, if possible a little more systematic and time spaced than in the MenC campaign however^{91,92}.

Only then will it be possible to study new suspected adverse reactions properly and to adequately counteract allegations of anti-vaccine movements. A problem is that one can not know what the next signal will be. International collaboration should be expanded, in order to

move towards a comprehensive safety surveillance network of childhood vaccination programmes. This may also help perform needed specific studies and increase scientific knowledge about adverse events following vaccinations. Eventually this will boost public confidence in the programmes.

For the coming year, if resources permit, are planned:

- implementation of a robust database system;
- accelerated annual report on 2002 and 2003;
- maintenance and evaluation of the current passive surveillance system;
- report on descriptive epidemiology of discoloured legs and follow up also with regard to the accelerated schedule;
- belated report on descriptive epidemiology of collapse reactions and follow up, also including the effect of the accelerated schedule;
- further exploration of possibilities of data linkage or sentinel studies, to test generated hypotheses;
- continuation of active study of incidence rates of some acknowledged but not so common adverse events following DPTP-Hib vaccinations, also in relation to the accelerated schedule with start of the programme at a younger age;
- active follow up of changes in the programme.

We plan to keep up a thorough high quality safety-surveillance-system and to stimulate reporting in the coming year. Thus, one can show that the vaccination programme is safe. The total of 1331 reports must be seen in relation to a total of 2.5 million vaccines administered with over 6 million components.

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Appendix 1 Vaccination Programme of 2001

BIJWERKINGEN

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

VACCINATIESCHEMA PER KIND

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

ENTADMINISTRATIES

De entadministratie wordt in het gehele land op geautomatiseerde wijze gevoerd. Voor inlichtingen met betrekking tot het Rijksvaccinatieprogramma en over de wijze van uitvoering kan men zich wenden tot de betreffende Provinciale Entadministraties. De GGD's van Amsterdam en Rotterdam zijn gelijkgesteld aan de Provinciale Entadministraties.

Provincie	Adres	Telefoon	Fax
GRONINGEN	Gerechtkade 8 9713 CA Groningen	050-3668350	050-3122733
FRIESLAND	Gerechtkade 8 9713 CA Groningen	050-3668350	050-3122733
DRENTHE	Lauwers 9.9405 BL Assen	0592-395260	0592-352169
OVERSSEL	v. Reeuwijkstraat 50, 7731 EH Ommen	0529-455717	0529-455805
FLEVOLAND	v. Reeuwijkstraat 50, 7731 EH Ommen	0529-455717	0529-455805
GEELDERLAND	Korte Coehoornstraat 2, 6811 LB Arnhem	026-4429242	026-4434999
UTRECHT	Zoutkampersdijk 7, 3432 TZ Nieuwegein	023-6081376	030-6081517
NRD-HOLLAND	Zeilmakerstraat 40, 1991 JC Velsen-Noord	023-5382454	023-5386822
AMSTERDAM	Nieuwe Achtergracht 100, 1018 WT Amsterdam	020-5555460	020-5555360
ZD-HOLLAND	Europaweg 141, 2711 EP Zoetermeer	079-3418238	079-3315047
ROTTERDAM	Schiedamsedijk 95, 3011 EN Rotterdam	010-4339652	010-4339652
ZEELAND	Naereboustraat 23, 4461 GR Goes	0113-224080	0113-224050
NFD-BRABANT	Boscheweg 57, 5056 KA Berkel-Enschot	013-5400588	013-5400056
LIMBURG	Dalderhaag 3, 6136 KM Sittard	046-4529910	046-4584479

Den Haag, december 2000

De Inspecteur-Generaal voor de Gezondheidszorg

prof. dr. J.H. Kingma



STAATSTOEZICHT OP DE VOLKSGEZONDHEID

Inspectie voor de Gezondheidszorg

RIJKS-VACCINATIEPROGRAMMA 2001

tegen:

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

2001	2000	1997	1992
DKTP	DKTP	DTP	DTP
+	+		+
Hib	+	BMR	BMR

1 ALGEMEEN

1.1 Organisatie

De uitvoering van de vaccinaties wordt verzorgd door onder andere thuiszorgorganisaties en GGD's, onder verantwoordelijkheid en medisch toezicht van de Provinciale Entadministraties en in overeenstemming met de richtlijnen van de Inspecteur-Generaal voor de Gezondheidszorg.

1.2 Vaccindistributie

De vaccins worden door de SVM (Stichting tot bevordering van de Volksgezondheid en Milieuhygiëne) afgeleverd aan de Provinciale Entadministraties. De distributie en het gebruik van de vaccins geschieden onder administratief toezicht van de Provinciale Entadministraties.

De verstrekking van de vaccins vindt uitsluitend plaats na aanvraag van de gebruiker(s) bij de Provinciale Entadministraties en onder voorwaarde dat de vaccins worden aangewend voor de uitvoering van het Rijksvaccinatieprogramma of in bijzondere omstandigheden volgens richtlijnen te geven door of namens de Minister van Volksgezondheid, Welzijn en Sport.

1.3 Registratie en verantwoording

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

1.4 Financiering

De kosten van de uitvoering van het Rijksvaccinatieprogramma komen ten laste van de in de AWBZ geregelde verzekering. Per verrichte enting wordt een bedrag uitbetaald aan de Provinciale Entadministraties. De Provinciale Entadministraties zullen volgens landelijke richtlijnen zorgdragen voor doorbetaling van de ter beschikking gestelde gelden aan de meewerkenden aan het Rijksvaccinatieprogramma. Voor vaccinaties in het kader van het Rijksvaccinatieprogramma door de thuiszorg of GGD behoeven de ouders geen bijdrage te betalen.

1.5 Kinderen tot 13 jaar die niet of niet volledig zijn ingeënt volgens het voor die jaarklasse geldende entschema, kunnen de nog **nodzakelijke** entingen kosteloos ontvangen in het kader van het Rijksvaccinatieprogramma. Dit geldt uitsluitend voor de DKTP-, DTP- en BMR-entingen.

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

1.6 Alle nadere regelingen welke met betrekking tot het Rijksvaccinatieprogramma 2001 worden getroffen, vereisen de goedkeuring van de Inspecteur-Generaal voor de Gezondheidszorg.

1.7 Exemplaren van deze folder kunnen worden aangevraagd bij de Inspectie voor de Gezondheidszorg, Postbus 16119, 2500 BC Den Haag, telefoon (070) 3405536.

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

2 ZUGELINGEN en KLEUTERS

Vaccinatieschema

- DKTP (Difterie - Kinkhoest - Tetanus - Poliomyelitis)

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

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

Let op

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

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

- Hib (Haemophilus influenzae type b)

Op de leeftijd van respectievelijk **2, 3 en 4 maanden** wordt één Hib-injectie gegeven. Er dient minimaal een tussenperiode van 4 weken in acht te worden genomen tussen de drie opeenvolgende vaccinaties. De vierde Hib-injectie wordt bij voorkeur op de leeftijd van 11 maanden gegeven. Er dient tenminste een tussenperiode van 6 maanden in acht te worden genomen tussen de derde Hib-injectie en de vierde Hib-injectie.
Doserings: 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.

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

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

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

- DTP (Difterie - Tetanus - Poliomyelitis)

De in 1997 geboren kinderen worden in 2001 gerevaccineerd met DTP-vaccin. Afhankelijk van de reeds vroeger gegeven entingen worden 1, 2 of 3 injecties gegeven (zie R.J.J.F. Burgmeijer en D.J.A. Bolscher "Vaccinaties bij kinderen", 3e herziene druk, Van Gorcum 1998).
Doserings: 1 ml INTRAMUSCULAIR.

3 SCHOOLKINDEREN

Vaccinatieschema

De in 1992 geboren kinderen worden in 2001 gerevaccineerd met DTP-vaccin. Afhankelijk van de reeds vroeger gegeven entingen worden 1, 2 of 3 injecties gegeven.
Doserings: 1 ml INTRAMUSCULAIR.

De in 1992 geboren kinderen krijgen in 2001 een BMR-injectie.
Doserings: 0,5 ml SUBCUTTAAN.

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

4 SIMULTANE VACCINATIES EN REGISTRATIE VAN PARTIJNUMMERS

Indien simultane vaccinaties (zoals DKTP + Hib, DTP + BMR) om een of andere reden niet simultaan worden gegeven, dient men tussen de vaccinaties de volgende intervallen aan te houden:

- een interval van tenminste 2 weken tussen de DK(ITP- en de Hib-entingen, ongeacht de volgorde waarin ze worden gegeven,
- na een DK(ITP-enting en/of een Hib-enting dient men 2 weken te wachten alvorens met BMR wordt gevaccineerd,
- na een BMR-enting dient men 4 weken te wachten alvorens men DK(ITP- of Hib-vaccin toedient.

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

Appendix 2 Package insert DPTP



RIJKSINSTITUUT
VOOR VOLKSGEZONDHEID
EN MILIEU



Poliomyelitisvaccin

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 poliocomponent bestaat uit geïnactiveerd en gezuiverd virus van de 3 typen: type 1 stam Mahoney, type 2 stam MEF I en type 3 stam Saukett. Aan het gecombineerde vaccin zijn als conserveermiddelen 2-fenoxyethanol en formaldehyde toegevoegd.

1 dosis (1 ml) bevat:

difterietoxoïde	≥ 30	IE *
kinkhoestvaccin	4	IE
tetanustoxoïde	≥ 60	IE
geïnactiveerd poliovirus:		
type 1	40	DE **
type 2	4	DE
type 3	7,5	DE
aluminiumfosfaat	1,5	mg
2-fenoxyethanol	5	mg
formaldehyde	25	µg

*) IE = Internationale Eenheid

**) DE = D-antigeeneenheden (eenheid voor poliocomponent)

Farmaceutische vorm en presentatie

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

Fabrikant en registratiehouder

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

RVG nummer

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

Indicatie

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

Contra-indicaties

- bekende overgevoeligheid voor bestanddelen van dit vaccin.
 - ernstige reactie na eerdere toediening van hetzelfde vaccin.
- Bij DKTP vaccin vormen de volgende reacties na eerdere toediening een contra-indicatie: convulsie, collaps en encephalopathie.

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

kan DTP vaccin worden gegeven volgens het DKTP entschema.

Speciale waarschuwingen en voorzorgen bij gebruik

Na enige tijd staan, ontstaat een bezinksel. Dit is een normaal verschijnsel en is niet van invloed op de kwaliteit van het vaccin. Alvorens het vaccin te gebruiken, moet het flesje enkele malen gezwenkt worden tot een homogene suspensie is verkregen. De kleur van het vaccin wordt veroorzaakt door de kleurstof fenolrood (pH-indicator) en mag variëren van oranjegeel tot oranje-rood. Indien de kleur duidelijk geel of violet is, mag het produkt niet worden gebruikt. De kleurindicator zegt niets over overschrijding van de bewaartemperatuur.

Dosering en de wijze van gebruik

Eén dosis DKTP vaccin is 1 ml en dient intramusculair te worden gegeven. Een volledige immunisatie bestaat uit een primaire serie van drie DKTP entingen en een eerste revaccinatie. De primaire serie wordt gegeven op de leeftijd van 3, 4 en 5 maanden, met een interval van minstens één maand.

De eerste revaccinatie ("DKTP-4") wordt tenminste 6 maanden na de laatste enting van de primaire serie gegeven, dus niet eerder dan op een leeftijd van 11 maanden. Dit schema wordt in het Rijksvaccinatie-programma 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. 030-2742424.

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.

Appendix 3 Package insert DTP



RIJKSINSTITUUT
VOOR VOLKSGEZONDHEID
EN MILIEU



Difterie-, Tetanus-,

Poliomyelitisvaccin

Beschrijving en samenstelling

DTP vaccin is een gecombineerd vaccin tegen difterie, tetanus en poliomyelitis. Difterie- en tetanustoxoïde zijn bereid uit toxines geproduceerd door respectievelijk *Corynebacterium diphtheriae*, stam Parke Williams nr. 8 en *Clostridium tetani*, stam Harvard 49205. De poliomyelitiscomponent bestaat uit geïnactiveerd en gezuiverd virus van de 3 typen: type 1 stam Mahoney, type 2 stam MEF I en type 3 stam Saukett. Aan het gecombineerde vaccin zijn als conserveermiddelen 2-fenoxylethanol en formaldehyde toegevoegd.

1 dosis (1 ml) bevat:

difterietoxoïde	≥ 5	IE *
tetanustoxoïde	≥ 20	IE
geïnactiveerd poliovirus:		
type 1	40	DE **
type 2	4	DE
type 3	7,5	DE
aluminiumfosfaat	1,5	mg
2-fenoxylethanol	5	mg
formaldehyde	0,025	mg

*) IE = Internationale Eenheid

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

Farmaceutische vorm en presentatie

DTP vaccin is een suspensie voor injectie en wordt afgevoerd in:

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

Fabrikant en registratiehouder

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

RVG nummer

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

Indicatie

Actieve immunisatie tegen difterie, tetanus en poliomyelitis.

DTP vaccin kan zowel voor primaire immunisatie (van volwassenen) als voor revaccinatie worden gebruikt.

Contra-indicaties

De algemene contra-indicaties die voor ieder vaccin gelden:

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

Speciale waarschuwingen en voorzorgen bij gebruik

Na enige tijd staan, ontstaat een bezinksel. Dit is een normaal verschijnsel en is niet van invloed op de kwaliteit van het vaccin.

Alvorens het vaccin te gebruiken, moet het flesje enkele malen gezwenkt worden tot een homogene suspensie is verkregen.

De kleur van het vaccin wordt veroorzaakt door de kleurstof fenolrood (pH-indicator)

en mag variëren van oranjegeel tot 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.

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 ongevacineerd 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 sessie, echter op verschillende injectieplaatsen. Als hiervan geen gebruik wordt gemaakt, dient een tussentijd te worden aangehouden van tenminste 2 weken indien DTP vaccin vóór de BMR vaccinatie is gegeven en van 4 weken indien DTP vaccin na de BMR vaccinatie wordt gegeven.

Ongewenste bijwerkingen

Lokale reacties kunnen voorkomen.

Algemene reacties als malaise en koorts zijn weinig frequent.

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

Bewaring

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

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

Uiterste gebruiksdatum

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

Appendix 4 Package insert Hib



RIJKSINSTITUUT
VOOR VOLKSGEZONDHEID
EN MILIEU



Haemophilus b conjugaat (PRP-T) vaccin **Haemophilus influenzae type b conjugaat vaccin gevriesdroogd**

Geproduceerd door Pasteur Mérieux sv. - Lyon - France

Beschrijving en samenstelling

Haemophilus influenzae type b conjugaat (PRP-T) vaccin, afgekort als Hib (PRP-T) vaccin, is een gevriesdroogd vaccin waarbij het kapselpolysaccharide, polyribosylribitol-fosfaat (PRP), geconjugeerd is met tetanus-toxoid als dragereiwit. Het vaccin wordt geresuspendeerd met de bijgepakte reconstitutievlloeistof (0,4 % natriumchloride oplossing).

Het gevriesdroogde vaccin bevat:

- polysaccharideconjugaat met tetanus-toxoid (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 injectievlloeistof en wordt afgevuld in flesjes à 1 dosis en verpakt met evenveel flesjes reconstitutievlloeistof bestelnr. 380

Fabrikant

Pasteur Mérieux sérums et vaccins

Registratiehouder

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

RVG nummer

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

Indicaties

Actieve immunisatie van zuigelingen en peuters tegen invasieve infecties veroorzaakt door Haemophilus influenzae type b: meningitis, sepsis, cellulitis, arthritis en epiglottitis.

Immunisatie van gezonde kinderen ouder dan 5 jaar en van volwassenen wordt niet aanbevolen.

Contra-indicaties

Overgevoeligheid voor een bestanddeel van het vaccin, in het bijzonder voor tetanuseiwit.

Speciale waarschuwingen en voorzorgen bij gebruik

Zoals bij elke vaccinatie wordt geadviseerd het inspuiten van Hib (PRP-T) vaccin uit te stellen bij koorts of bij een acute infectie. Hib (PRP-T) vaccin mag niet intraveneus worden toegediend.

Alhoewel er tot op heden geen anafylactische reacties tengevolge van het vaccin werden vastgesteld, verdient het aanbeveling om een epinefrine-injectie en corticosteroiden beschikbaar te hebben en zodig, gedoseerd naar leeftijd en lichaamsgewicht, toe te dienen.

Hib (PRP-T) vaccin beschermt niet tegen infecties veroorzaakt door andere sero-

types van *Haemophilus influenzae* dan serotype b, noch tegen meningitis veroorzaakt door andere micro-organismen. In geen enkel geval kan het tetanus-eiwit van het vaccin de gewone anti-tetanus vaccinatie vervangen.

Interacties met andere geneesmiddelen en andere vormen van interactie

Als Hib (PRP-T) vaccin wordt toegediend aan patiënten met maligne aandoeningen of patiënten die met immunosuppressieve geneesmiddelen worden behandeld, of anderszins immunodeficiënt zijn, kan de verwachte immuunrespons uitblijven.

Dosering en de wijze van toediening

Gebruik voor resuspensie uitsluitend de bijgeleverde reconstitutievloeistof. Resuspensie geschiedt door 0,6 ml van de reconstitutievloeistof met een steriele spuit bij het gedroogde vaccin te voegen. Door het product voorzichtig om te zwenken ontstaat een heldere, kleurloze oplossing. Eén dosis bestaat uit 0,5 ml vaccin, ongeacht de leeftijd. Het vaccin dient binnen een uur intramusculair te worden toegediend.

Vaccinatieschema:

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

In het Rijksvaccinatieprogramma wordt Hib (PRP-T) vaccin gelijktijdig op twee verschillende injectieplaatsen met DKTP vaccin toegediend op de leeftijd 2, 3 en 4 maanden, gevolgd door een herenting tenminste 6 maanden later.

Gecombineerde toediening van Hib (PRP-T) vaccin en DKTP vaccin in één spuit is niet toegestaan.

Gebruik gedurende zwangerschap en het geven van borstvoeding

Het toedienen van Hib (PRP-T) vaccin tijdens de zwangerschap wordt ontraden.

Bijwerkingen

Na injectie van Hib (PRP-T) vaccin kunnen lokale reacties voorkomen, zoals pijn, roodheid en zwelling. In een aantal gevallen treedt koorts op. Ernstige algemene reacties zijn niet bekend.

Artsen wordt verzocht mogelijke bijwerkingen te melden aan de afdeling Klinisch Onderzoek van het Laboratorium voor Veldonderzoek Vaccins van het RIVM, tel.nr.: 030 - 274 2424.

Bewaring

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

Uiterste gebruiksdatum

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

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

Appendix 5 Package insert MMR



RIJKSINSTITUUT
VOOR VOLKSGEZONDHEID
EN MILIEU



Bof-, Mazelen-, Rubellavaccin levend, gevriesdroogd

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

Beschrijving en samenstelling

Bof-, mazelen-, rubellavaccin (BMR vaccin) is een gevriesdroogd preparaat van levend, verzwakte bof-, mazelen- en rode hond (= rubella) virussen.

Bofvirus, stam Jeryl Lynn, is gekweekt op kippenembryo-fibroblasten; mazelenvirus, stam Moraten, is gekweekt op kippen-embryo-fibroblasten en wordt verkregen door de reeds verzwakte Edmonston stam door herhaalde passage in celculturen verder te verzwakken en rubellavirus, stam Wistar RA27/3, is gekweekt op menselijke diploïde celculturen (WI-38).

1 dosis (0,5 ml) bevat na resuspensie met de bijgepakte reconstitutievloeistof:

bofvirus ≥ 5000 p.f.u.*

mazelenvirus ≥ 1000 p.f.u.

rubellavirus ≥ 1000 p.f.u.

Sorbitol en gehydrolyseerde gelatine zijn als stabilisatoren aan het vaccin toegevoegd.

Het vaccin bevat geen antibiotica en geen conserveermiddel.

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

Farmaceutische vorm en presentatie

BMR vaccin is een poeder voor injectie-vloeistof en wordt afgevuld in:

flesjes à 1 dosis, met even zoveel flesjes

reconstitutievloeistof bestelnr. 442

11
gewoon water

Fabrikant en registratiehouder

RIVM, Postbus 1, 3720 BA Bilthoven

afd. verkoop SVM

Postbus 457, 3720 AL Bilthoven

Tel.: 030-2748010

RVG nummer

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

Indicatie

Actieve immunisatie tegen bof, mazelen en rubella vanaf de leeftijd van 14 maanden.

In het Rijksvaccinatie programma (RVP) wordt BMR vaccin tweemaal gegeven: vanaf de leeftijd van 14 maanden en in het 9de levensjaar.

Contra-indicaties

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

Speciale waarschuwingen en voorzorgen bij gebruik

- Bof- en mazelenvirus worden gekweekt in cellen afkomstig van kippenembryo's. Overgevoeligheid voor kippeneiwit is geen contra-indicatie; bij patiënten die bekend zijn met anafylactoïde reacties op kippeneiwit kunnen BMR vaccinaties onder de gebruikelijke voorzorgen worden uitgevoerd volgens de instructie in het Rijksvaccinatie programma. Tevens wordt geadviseerd epinefrine injectie en corticosteroiden beschikbaar te hebben en zonodig, gedoseerd naar leeftijd en/of lichaamsgewicht, toe te dienen.
- Bij HIV-patiënten met ernstige immuun-deficiëntie komen BMR vaccinatie gerelateerde complicaties voor. Aan hen wordt BMR vaccin dan ook niet toegediend; bij contacten van dergelijke patiënten met mazelen wordt profylaxe aanbevolen met normaal immunoglobuline. Bij HIV-geïnfecteerde patiënten met een lichte tot matige immuun-deficiëntie kan BMR vaccinatie aangewezen zijn ter voorkoming van vaak fataal verlopende mazelen bij deze patiënten.
- Voor gelijktijdig toedienen van vaccins zie onder dosering en de wijze van gebruik.
- Contraceptieve maatregelen moeten worden genomen tot 3 maanden na vaccinatie van vruchtbare vrouwen.
- Aanbevolen wordt vaccinatie tegen BMR minstens 3 maanden uit te stellen na transfusie met totaal bloed of plasma en na toediening van immunoglobuline afkomstig van de mens.

Dosering en de wijze van gebruik

Gebruik voor resuspensie uitsluitend de bijgeleverde reconstitutievloeistof, omdat deze vrij is van conservantia of andere virusinactiverende middelen. Resuspensie geschiedt door 6 ml (multidoses) of 0,6 ml (monodosis) van de reconstitutievloeistof

met een steriele spuit bij het gedroogde vaccin te voegen. Omdat het flesje met vaccin onder vacuüm 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 Rijksvaccinatie programma voorziet in vaccinatie op een leeftijd van 14 maanden en een tweede vaccinatie op circa 9-jarige leeftijd. Alhoewel de effectiviteit van BMR vaccinaties in het eerste levensjaar (tot en met de twaalfde levensmaand) niet in klinische studies is onderzocht, kan het in bepaalde gevallen wenselijk zijn de BMR vaccinatie eerder te geven. Kinderen die BMR vaccin kregen voor de leeftijd van 12 maanden, moeten opnieuw worden gevaccineerd na de leeftijd van 14 maanden. Vaccinatie vóór de leeftijd van 6 maanden wordt afgeraden.

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

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

Ook volwassenen kunnen met BMR vaccin worden geïmmuniseerd. Dan is een éénmalige toediening van BMR vaccin voldoende.

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. 030-2742424.

Bewaring

Het produkt dient bij 2 - 8 °C te worden bewaard; beschermen tegen licht.

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

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

Uiterste gebruiksdatum

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

Appendix 6 Package insert aK



**INFORMATIE
VOOR DE OUDERS
OF VERZORGERS**



**INFORMATIE
VOOR DE ARTS**



Acellulair kinkhoestvaccin

Acellulair kinkhoestvaccin

1. ALGEMENE INFORMATIE

1.1. Lees eerst deze bijsluiter

Lees de informatie in deze bijsluiter vóórdat acellulair kinkhoestvaccin wordt toegediend. Het is goed om van tevoren te weten waarom acellulair kinkhoestvaccin wordt toegediend (zie punt 2), waar u op moet letten (zie 3 en 4) en wanneer het vaccin beter niet toegediend kan worden (zie 3). Het is ook goed om te weten dat u of uw kind soms voor korte tijd wat last kan hebben van vaccinatie met een vaccin (zie punt 5).

Bij vragen of onduidelijkheden over de inhoud van deze bijsluiter kunt u zich altijd tot uw arts of apotheker wenden.

1.2. Naam van het geneesmiddel

Acellulair kinkhoestvaccin.

1.3. Wat is de samenstelling van acellulair kinkhoestvaccin?

Werkzame stoffen

Een dosis van het vaccin (0,5 ml) bevat ten minste 25 µg pertussistoxoïde, 25 µg filamenteuze hemagglutinine en 8 µg pertactine.

Hulpstoffen

Aluminiumzouten, 2-fenoxylethanol, natriumchloride, water voor injectie.

1.4. Hoe ziet acellulair kinkhoestvaccin er uit en wat is de inhoud van de verpakking?

Acellulair kinkhoestvaccin wordt geleverd als troebele witte suspensie in een injectieflacon. Het vaccin wordt geleverd in verpakkingen die 50 flesjes bevatten.

1.5. Tot welke geneesmiddelen-groep behoort acellulair kinkhoestvaccin?

Acellulair kinkhoestvaccin is een kinkhoestvaccin. In het vaccin zitten kleine hoeveelheden van delen van de kinkhoestbacterie (het antigeen) die kinkhoest veroorzaakt. Uw kind kan hiervan niet ziek worden, maar als uw kind hiermee wordt ingeënt, maakt het lichaam afweerstoffen.

1.6. Wie is verantwoordelijk voor het in de handel brengen van acellulair kinkhoestvaccin in Nederland?

GlaxoSmithKline B.V.; Huis ter Heideweg 62, 3705 LZ Zeist

1.7. Onder welk nummer is acellulair kinkhoestvaccin in het Register ingeschreven?

Acellulair kinkhoestvaccin is in het Register ingeschreven onder RVG 22335

2. WAARVOOR WORDT ACELLULAIR KINKHOESTVACCIN GEBRUIKT?

Acellulair kinkhoestvaccin is bestemd voor kinderen tot 6 jaar die niet eerder tegen kinkhoest zijn gevaccineerd volgens het basisimmunisatieschema van het Rijksvaccinatieprogramma (zie ook rubriek 4.1. Wat is de dosering van acellulair kinkhoestvaccin).

Tevens kan het vaccin worden gebruikt voor een zgn. revaccinatie van kinderen tot 6 jaar die genoemd basisimmunisatieschema van het Rijksvaccinatieprogramma hebben doorlopen.

3. WAAR MOET OP GELET WORDEN VOORDAT ACELLULAIR KINKHOESTVACCIN WORDT TOEGEDIEND?

3.1. Wanneer mag acellulair kinkhoestvaccin niet worden toegediend?

- Als uw kind overgevoelig is voor één van de bestanddelen van het vaccin of als uw kind ongewoon of allergisch heeft gereageerd op een eerdere injectie met acellulair kinkhoestvaccin.
- Vaccinatie moet worden uitgesteld als uw kind een infectie heeft met hoge koorts.
- Als uw kind lijdt aan een voortschrijdende aandoening van het centrale zenuwstelsel of als uw kind na een eerdere injectie met een kinkhoestvaccin last kreeg van stuipen, flauw viel of een hersenaandoening kreeg.

3.2. Welke bijzondere voorzorgen gelden er bij het gebruik van acellulair kinkhoestvaccin?

Algemene voorzorgen

Licht uw arts in als uw kind na eerdere toediening van een vaccin tegen kinkhoest ziek werd en daarbij verschijnselen optraden zoals:

- binnen 48 uur na vaccinatie een lichaamstemperatuur hoger dan 40,5 °C;
- binnen 48 uur na vaccinatie flauwvallen of een op shock gelijkende toestand;
- binnen 48 uur na vaccinatie onophoudelijk huilen langer dan 3 uur;
- stuipen binnen 3 dagen na vaccinatie.

Voorzorgen in verband met de aanwezigheid van hulpstoffen
Niet van toepassing.

KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING

Acellulair kinkhoestvaccin bevat drie gezuiverde pertussisantigenen [pertussistoxoïde (PT), filamenteuze hemagglutinine (FHA) en 69 kiloDalton proteïne van de buitenmembraan (pertactine)], geadsorbeerd aan aluminiumzouten.

Eén dosis vaccin van 0,5 ml bevat ten minste 25 µg PT, 25 µg FHA en 8 µg pertactine.

KLINISCHE GEGEVENS

Therapeutische indicaties

Acellulair kinkhoestvaccin is bestemd voor kinderen tot 6 jaar die niet eerder tegen pertussis (kinkhoest) zijn gevaccineerd volgens het basisimmunisatieschema van het Rijksvaccinatieprogramma.

Tevens kan acellulair kinkhoestvaccin als boostervaccin worden gegeven aan kinderen tot 6 jaar die het volledige basisimmunisatieschema van het Rijksvaccinatieprogramma hebben doorlopen.

Dosering en wijze van toediening

Dosering

Zuigelingen en kinderen tot 6 jaar die niet eerder tegen pertussis (kinkhoest) zijn gevaccineerd volgens het basisimmunisatieschema van het Rijksvaccinatieprogramma dienen 3 immunisaties te krijgen met een interval van 2 maanden.

Revaccinatie van kinderen die een volledige basisimmunisatie hebben ontvangen met DKTP (met hele of acellulair kinkhoestvaccin) dient plaats te vinden vóór de leeftijd van 6 jaar, met een interval van ten minste 6 maanden na de basisimmunisatie.

Onder basisimmunisatie wordt verstaan:

De primaire immunisatie op de leeftijd van 2, 3 en 4 maanden, afgerond met een vierde immunisatie op de leeftijd van 11 maanden (7 maanden na de derde injectie van de primaire vaccinatie). Deze basisimmunisatie dient uitgevoerd te worden met een vaccin waarin naast pertussis componenten, tetanus, polio en difterie componenten zijn opgenomen.

Wijze van toediening

Acellulair kinkhoestvaccin is bij zuigelingen bestemd voor diepe intramusculaire injectie aan de anterolaterale kant van de dij. Bij oudere kinderen dient het vaccin in de musculus deltoides worden toegediend.

Elke volgende dosis dient bij voorkeur op een andere plaats te worden toegediend. Een dunne naald kan worden gebruikt voor vaccinatie alsmede het uitvoeren gedurende ten minste twee minuten van een stevige druk (zonder te wrijven) op de plaats van injectie.

Acellulair kinkhoestvaccin mag in geen geval intravasculair worden toegediend.

Contra-indicaties

Net als bij andere vaccins dient toediening van acellulair kinkhoestvaccin te worden uitgesteld als een kind lijdt aan een acute, ernstige, met koorts gepaard gaande ziekte. Een lichte infectie vormt echter geen contra-indicatie voor vaccinatie.

Acellulair kinkhoestvaccin mag niet worden toegediend aan kinderen van wie bekend is dat ze overgevoelig zijn voor één of meerdere bestanddelen van het vaccin, of aan kinderen die bij een eerdere toediening van acellulair kinkhoestvaccin tekenen van overgevoeligheid hebben vertoond.

Acellulair kinkhoestvaccin mag niet worden toegediend aan kinderen met progressieve neurologische aandoeningen of aan kinderen bij wie de volgende reacties na eerdere toedieningen zijn opgetreden: convulsies, collaps en encephalopathie.

Speciale waarschuwingen en bijzondere voorzorgen bij gebruik

Alvorens tot vaccinatie wordt overgegaan, dient een controle van de medische geschiedenis en een klinisch onderzoek van de patiënt/het kind plaats te vinden. Dit vooral met betrekking tot eerdere vaccinatie en het eventueel optreden van bijwerkingen.

Indien zich tijdelijk één of meerdere van de volgende verschijnselen voordoen na toediening van een vaccin dat acellulair of hele cel pertussisantigenen bevatte, dient een zorgvuldige afweging te worden gemaakt alvorens te besluiten tot toediening van volgende doses die de pertussiscomponent bevat.

In bepaalde gevallen, zoals een hoge incidentie van kinkhoest, kunnen de mogelijke voordelen zwaarder wegen dan de mogelijke risico's, vooral omdat bij de genoemde verschijnselen geen sprake is van blijvende gevolgen.

De volgende verschijnselen werden vroeger als contra-indicaties voor DTPw aangemerkt en kunnen nu als algemene voorzorgsmaatregelen worden beschouwd.

- binnen 48 uur een temperatuur van $\geq 40,5^{\circ}\text{C}$, hetgeen niet te wijten is aan een andere bekende oorzaak;
- binnen 48 uur flauwvallen of een op shock gelijkende toestand (episoden van hypotonie en hyporespons);
- binnen 48 uur aanhoudend, onroostbaar huilen gedurende 3 uur of langer;
- binnen 3 dagen na vaccinatie stuipen met of zonder koorts.

Zoals met alle injecteerbare vaccins dient te allen tijde adequate medische behandeling beschikbaar te zijn voor het geval dat zich na toediening van het vaccin anafylactische reacties voordoen. Daarom dienen gevaccineerde kinderen na immunisatie 30 minuten onder medisch toezicht te blijven.

Er zijn onvoldoende gegevens om het gebruik van acellulair kinkhoestvaccin buiten het schema zoals gespecificeerd onder rubriek 4.2. te ondersteunen.

Voorzichtigheid dient te worden betracht bij de toediening van acellulair kinkhoestvaccin aan kinderen met trombocytopenie of abnormale bloedingen, omdat bij hen na intramusculaire toediening bloedingen kunnen ontstaan.

Koortstuipen in de anamnese, convulsies in de familie-anamnese, wiegedood (S.I.D.S.) in de familie-anamnese en bijwerkingen in de familie-anamnese, vormen geen contra-indicatie na vaccinatie met pertussis bevattende vaccins.

HIV-infectie wordt niet beschouwd als een contra-indicatie voor vaccinatie tegen pertussis. Het is mogelijk dat de verwachte immunologische reactie niet wordt bereikt na inenting bij patiënten met immunosuppressie, b.v. patiënten die een behandeling met immunosuppressiva krijgen.

Interacties met andere geneesmiddelen en andere vormen van interactie
Acellulair kinkhoestvaccin kan gelijktijdig worden toegediend met andere geïnactiveerde kindervaccins. Er zijn geen gegevens beschikbaar over de interactie van acellulair kinkhoestvaccin met BMR vaccins. Gelijktijdige vaccinatie wordt daarom afgeraden.

Acellulair kinkhoestvaccin mag niet in één spuit met meerdere vaccins worden toegediend. Indien tegelijkertijd meerdere vaccins moeten worden toegediend, dienen de injecties op verschillende plaatsen te worden gegeven.

Evenals bij andere vaccins is het te verwachten dat bij patiënten die een immunosuppressieve behandeling krijgen of een immunodeficiëntie hebben geen adequate immunologische respons wordt bereikt.

FARMACEUTISCHE GEGEVENS

Lijst van hulpstoffen

Aluminiumzouten, 2-fenoxyethanol, natriumchloride, water voor injectie.

Gevalen van onverenigbaarheid

Het vaccin mag niet met andere vaccins in dezelfde injectiespuit worden gemengd.

Houdbaarheid

De uiterste gebruiksdatum van het vaccin staat vermeld op het etiket en de verpakking voorafgegaan door de woorden 'Niet te gebruiken na' of 'Exp.'. 'Exp.' staat voor vervaldatum. Na deze datum mag het vaccin niet meer worden gebruikt. Mits bewaard bij de voorgeschreven temperatuur van +2 °C tot +8 °C, kan het vaccin 3 jaar worden bewaard.

Speciale voorzorgsmaatregelen bij opslag

Acellulair kinkhoestvaccin dient bij een temperatuur tussen de +2 °C en +8 °C te worden bewaard.

Het vaccin mag niet worden ingevroren. Gebruik het vaccin niet als het bevroren is geweest.

Aard en inhoud van de verpakking

Acellulair kinkhoestvaccin wordt geleverd als troebele witte suspensie in een injectieflacon. Bij opslag kan een witte neerslag met heldere bovenstaande vloeistof worden waargenomen.

De injectieflacons zijn gemaakt van neutraal glas, type I, dat voldoet aan de eisen van de Europese Farmacopee.

Instructies voor gebruik en verwerking

Het vaccin dient vóór gebruik goed te worden geschud om een homogene, troebele suspensie te verkrijgen, en visueel te worden gecontroleerd op vreemde deeltjes en/of verandering in fysiek uiterlijk. Mocht één van deze verschijnselen worden waargenomen, gooi het vaccin dan weg.

Naam en permanent adres of officiële vestigingsplaats van de houder van de vergunning voor het in handel brengen

GlaxoSmithKline B.V.; Huis ter Heideweg 62, 3705 LZ Zeist

3.3. Kunt u acellulair kinkhoestvaccin samen met andere geneesmiddelen gebruiken?

Als uw kind andere geneesmiddelen gebruikt of onlangs heeft gebruikt, raden wij u aan uw arts of apotheker hierover te informeren voordat uw kind met de therapie begint. Verschillende geneesmiddelen kunnen namelijk elkaars werking beïnvloeden.

Indien de werking van het afweersysteem van uw kind is verminderd of als uw kind hiervoor behandeld wordt, bestaat de mogelijkheid dat acellulair kinkhoestvaccin een minder goede bescherming geeft.

Het vaccin kan gelijktijdig worden toegediend met andere vaccins doch mag niet met andere vaccins in een 1 injectiespuit worden gemengd.

4. AANWIJZINGEN VOOR HET GEBRUIK VAN ACELLULAIR KINKHOESTVACCIN

4.1. Wat is de dosering van acellulair kinkhoestvaccin?

Als uw kind nog niet volgens het basisimmunisatieschema* van het Rijksvaccinatieprogramma tegen kinkhoest is gevaccineerd, bestaat een volledige kuur bij zuigelingen en kinderen tot de leeftijd van 6 jaar uit 3 injecties met het acellulair kinkhoestvaccin. Tussen deze injecties dient een periode van ten minste 2 maanden in acht te worden genomen.

Als uw kind genoemd basisimmunisatieschema* heeft doorlopen dient op latere leeftijd een zogenaamde revaccinatie plaats te vinden. Deze bestaat uit één dosis acellulair kinkhoestvaccin. Deze dosis dient minimaal 6 maanden na de laatste injectie van het basisimmunisatieschema* doch vóór het bereiken van de leeftijd van 6 jaar te worden toegediend.

*: In dit schema ontvangt uw kind drie injecties met een vaccin dat uw kind beschermt tegen difterie, kinkhoest, tetanus en polio (de zgn. DKTP-injecties). Deze injecties worden gegeven 2, 3 en 4 maanden na de geboorte. Voor langdurige bescherming krijgt uw kind op de leeftijd van 11 maanden nog een vierde dosis. Hiermee is de zgn. basisimmunisatie afgerond.

4.2. Gebruiksaanwijzing

Acellulair kinkhoestvaccin dient vóór het gebruik goed te worden geschud. Het vaccin dient door degene die het vaccin toedient goed gecontroleerd op vreemde deeltjes of zichtbare veranderingen. Het vaccin mag niet in één spuit met andere vaccins worden toegediend.

- Acellulair kinkhoestvaccin wordt in een spier gespoten, meestal in het bovenbeen of bovenarm en bij voorkeur steeds op een andere plek;
- Het vaccin mag **nooit direct in een ader worden ingespoten**;
- Zoals met alle vaccins die worden ingespoten dient altijd medische behandeling beschikbaar te zijn voor het geval zich na het inspuiten van het vaccin ongewenste overgevoeligheidsreacties voordoen (herkenbaar aan verschijnselen als jeukende uitslag op de handen of voeten, het opzwellen van de ogen en het gezicht en problemen met ademen of slikken);
- Indien er meerdere vaccins tegelijkertijd moeten worden toegediend, dienen de injecties op verschillende plaatsen te worden gegeven.

Mocht u een afspraak voor een vervolg-injectie zijn vergeten, raadpleeg dan uw arts, GGD of het vaccinatiebureau.

5. MOGELIJKE BIJWERKINGEN VAN ACELLULAIR KINKHOESTVACCIN

Zoals bij elk ander vaccin kan het zijn dat uw kind pijn of last krijgt op de plaats waar de injectie is toegediend. Ook kan die plek rood worden of opzwellen. Deze reacties treden meestal op binnen twee dagen. Een enkele keer kunnen deze na ~~5 tot 8 dagen~~ terugkomen.

Andere reacties die kunnen voorkomen, zijn koorts, verminderde eetlust, rusteloosheid, buitensporig huilen, braken en diarree. Als deze verschijnselen niet overgaan of erger worden, licht dan uw arts in.

Na inenting zijn soms nog andere verschijnselen gemeld. Hierbij gaat het om ademhalingsstoornissen, huidontsteking en middenoorontsteking, infecties van de bovenste luchtwegen, hoesten en bronchitis.

Bij elk vaccin bestaat er na injectie een kans op een overgevoeligheidsreactie. Om die reden dient uw kind na toediening van een vaccin per injectie gedurende 30 minuten onder medisch toezicht te blijven.

Waarschuw tevens uw arts of apotheker indien een bijwerking optreedt die niet in deze bijsluiting wordt vermeld of als de in de bijsluiting vermelde bijwerkingen ernstig zijn.

6. HOE MOET ACELLULAIR KINKHOESTVACCIN WORDEN BEWAARD EN WAT IS DE UITERSTE GEBRUIKSTERMIJN?

De uiterste gebruiksdatum staat op het etiket en de verpakking vermeld, voorafgegaan door de woorden: 'Niet te gebruiken na'. Na deze datum mag het vaccin dus niet meer worden gebruikt.

Bewaar het vaccin in de koelkast (2 - 8 °C), maar nooit in het vriesvak. Bewaar acellulair kinkhoestvaccin buiten het bereik van kinderen.

7. WANNEER IS DEZE BIJSLUITER VOOR HET LAATST GEWIJZIGD?

Januari 2002