Adverse Events in the Netherlands Vaccination Programme

Reports in 2010 and Review 1994-2010
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Colophon

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P.E. Vermeer-de Bondt, Centre for Infectious Disease Control Netherlands
N. Moorer-Lanser, Centre for Infectious Disease Control Netherlands
T.A.J. Phaff, Centre for Infectious Disease Control Netherlands
B. Oostvogels, Centre for Infectious Disease Control Netherlands
C. Wesselo, Centre for Infectious Disease Control Netherlands
N.A.T. van der Maas, Centre for Infectious Disease Control Netherlands

Contact:
P.E.Vermeer-de Bondt
Preparedness and Response Unit-LCI
patricia.vermeer@rivm.nl

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Abstract

Adverse Events in the Netherlands Vaccination Programme
Reports in 2010 and Review 1994-2010

In 2010, 800,000 children received one or more vaccines on 1.3 million dates, with more than 7 million vaccine components. There is always some chance of adverse reactions but these are usually not severe, though sometimes frightening. This year, RIVM received 1380 reports of adverse events following immunisation (AEFI). This is 16% less than in 2009 when 2 vaccination campaigns raised considerable adverse publicity with subsequent increase in reports. Data show that the benefit of the vaccination programme outweighs the risk of adverse reactions by far.

Safety surveillance: necessary part of the vaccination programme
Enhanced safety surveillance has been an integral part of the vaccination programme since 1962. Annual reports have been published since 1983, following independent re-evaluation. The surveillance system of the Netherlands enjoys very high reporting rates and is highly sensitive for signals. It allows individual follow-up because of name-based reporting. In this last year of safety surveillance in this setting, we present an overview of results since 1994. This brings some new insights.

Careful reporting and validation system
All reports were validated and complemented, preferably also with eyewitness accounts (92%). Final assessment followed according to case definitions and causality criteria. The embedding of the safety surveillance in the telephone consultation service has contributed to the quality of the reports.

Reported adverse events
In 2010, 78% of reports (1082) had possible causal relation with the vaccination. These concerned major adverse reactions in 48% (523), including very high fever (≥40.5 °C), persistent screaming, collapse, discoloured legs, febrile convulsions or atypical attacks with chills, myoclonics or hyper/hypo-tonicity. Altogether 22% (296) of reports were chance occurrences. Reported severe infections and epilepsy had no causal relation with the vaccinations. In addition, none of the 5 reports on death was related to vaccination. An independent expert committee has reassessed these severe adverse events.

Keywords:
adverse event following immunisation, AEFI, vaccination programme, safety surveillance, childhood vaccines, immunisation
Rapport in het kort

**Bijwerkingen van het Rijksvaccinatieprogramma**
Meldingen in 2010 en overzicht 1994-2010

In 2010 kregen 800.000 kinderen in Nederland vaccinaties binnen het Rijksvaccinatieprogramma (RVP). In het totaal is ruim 1,3 miljoen keer gevaccineerd, met meer dan 7 miljoen vaccins – de meeste prikken bevatten meerdere vaccins. Dit jaar zijn 1380 vermoede bijwerkingen gemeld. Dat is 16 procent minder dan in 2009, een jaar waarin de twee grootschalige vaccinatiecampagnes tegen baarmoederhalskanker en pandemische griep aanzienlijke onrust veroorzaakten, waardoor het aantal meldingen van bijwerkingen toenam. De grote gezondheidswinst van het RVP weegt op tegen de bijwerkingen, ook al zijn deze soms heftig en schrikaanjagend.

**Veiligheidsbewaking: noodzakelijk onderdeel RVP**

**Zorgvuldig meldings- en validatiesysteem**
Alle meldingen worden gevalideerd en aangevuld met gegevens die nodig zijn om een juist beeld van de situatie te krijgen. Dit gebeurt bij voorkeur ook met een ooggetuigenverslag (92 procent). Daarna worden de meldingen getoetst aan definities voor diagnoses en wordt beoordeeld of er een oorzakelijk verband is met de vaccinaties. De telefonische adviesdienst is een belangrijk instrument van de bijwerkingenbewaking en heeft aanzienlijk bijgedragen aan de kwaliteit van de meldingen.

**Gemelde bijwerkingen**
In 2010 werd 78 procent (1082) van de meldingen daadwerkelijk als bijwerking beschouwd. Daarvan betrof het in 48 procent (523) zogenoemde major ziektebeelden, zoals zeer hoge koorts (vanaf 40,5 °C), langdurig huilen, collapserecties, verkleurde benen, koortsstuipten of atypische aanvallen met rillingen, schrikschokken, gespannenheid of slapte. Bij 296 meldingen (22 procent) was er een toevallige samenloop van omstandigheden en geen oorzakelijk verband met de vaccinatie. Ook de gemelde ernstige infecties en epilepsie stonden los van de vaccinaties. Bij de vijf kinderen die na een vaccinatie zijn overleden, zijn de vaccinaties daarvan evenmin de oorzaak geweest. Dergelijke ernstige beelden zijn herbeoordeeld door een groep van externe deskundigen.

Trefwoorden:
bijwerking, rijksvaccinatieprogramma, vaccinaties, veiligheidsbewaking, RVP
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Summary

The National Institute for Public Health and Environment (RIVM) has monitored adverse events following immunisation (AEFI) under the Netherlands Vaccination Programme (RVP) of the Netherlands since 1962. From 1984 until 2003, evaluation was done in close collaboration with the Health Council (GR). A RIVM expert panel gave reassessments of selected adverse events from 2004 onwards. The telephone service for reporting and consultation is an important tool for this enhanced passive surveillance system. RIVM reports fully, on all incoming reports in a calendar year, irrespective of causal relation, since 1994. This report on 2010 is the seventeenth annual report. It will be the last report in the series because the adverse event registration of the RVP has been transferred to Lareb in 2011. Therefore, this report will not only present the results of 2010 but also give a survey over the period 1994-2010.

In 2010 as before, the majority of reports (84%) came in by telephone giving the chance to clarify, guide and advise. Child Health Care professionals continue to be the main reporters (81%). Parents, General Practitioners (GP), hospital or other medical staff provided additional data on request (85%). The proportion reports with only one information source decreased over the years from 50% to 10-15% of reports since 2004. Data presented in the current report are based on (working) diagnoses by RIVM using case definitions, after supplementation and verification of information. Assessment of causality is included in the classification of reports.

In 2010, RIVM received altogether 1380 adverse events, involving 1260 children. This year, 800,000 children have been vaccinated on more than 1.3 million vaccination dates. These vaccinees received over 7 million vaccine components.

The overall AE reporting rate is 158 reported children per 100,000 children vaccinated (once or more) with a rate of 104 reports per 100,000 vaccination dates. Reporting rates differ considerably per vaccine dose and are highest for the infants.

Of the reports in 2010, only 2 were non-classifiable because of missing information; both cases concerned non-severe events. Of 1378 classifiable events 1082 (79%) were considered to be possibly, probably or definitely causally related with the vaccination (adverse reactions) and 296 (21%) were considered coincidental events. This is in accordance with other years.

739 AEFI were classified as so-called ‘minor’ local, skin or systemic events, of which 540 (73%) were considered possible adverse reactions. So-called ‘major’ adverse events totalled 641, including events grouped under fits, faints, discoloured legs, persistent screaming, major-illness, and death (with inclusion of 136 severe local reactions and 3 major skin manifestations). Of these major AEFI, 542 (85%) were assessed as possible adverse reaction. Discoloured legs were reported 98 times with possible causal relation in all but 2. Collapse (HHE) occurred 91 times, 9 times considered unrelated. All 4 reported breath-holding-spells were assessed as causally related. 69 Times fainting occurred in older children, only 1 unrelated. Convulsions were diagnosed in 57 cases, in all but 8 with fever, mainly occurring in the 1-year olds. 41 Convulsions were considered causally related. Atypical attacks (24) had possible causal relation in 13 cases. Epilepsy (4) was considered a chance occurrence in all instances. Persistent screaming was reported 53 times, in all but 2 considered causally related.

In the major general illness category, very high fever (≥40.5 °C) was the working diagnosis in 49 reports and another 6 children had very high fever with rash after MMR (‘vaccinitis’). 2 Children had extreme hypothermia without noted fever before. Of these 57 reports, 44 were with inferred causality. Of the other 43 major-illness cases, 9 had a possible causal relation (Idiopathic Thrombocytopenic Purpura-ITP-4, apnoea/decreased saturation-2, complicated migraine-1, arthritis-1 and indirectly osteomyelitis-1). There were 3 abscesses, 2 after BCG (Bacille Calmette Guérin) vaccine.
In 2010, death was reported in 5 children; all were considered chance occurrences after thorough assessment. In 3 cases post-mortem examination was performed. Complications of infection were the cause of death in 3 children and in 2 death followed a derangement of a suspected, as yet undiagnosed, metabolic disorder. In none, the vaccination was considered to have played a role in precipitation of illness or causing a delay in treatment.

Most frequently (651) reports involved infant DTP-IPV-Hib vaccination (diphtheria, pertussis, tetanus, polio, *Haemophilus Influenzae* type b), in 97% simultaneously with Pneu (7-valent conjugated pneumococcal vaccine); DTP-IPV-Hib was combined with Hepatitis B vaccine in 124 cases (19%). 305 Reports concerned booster DTP-IPV at 4 years (8 times with other vaccines). MMR+MenC (measles, mumps and rubella; Meningococcus C) at 14 months, were involved 195 times, in 13% as single (catch up) doses (MenC or MMR), overall twice with simultaneous other vaccines. Of all reports, 82 concerned MMR+DT-IPV boosters at 9 years (with 5 times only DT-IPV) and 129 HPV (human papilloma virus), once with a simultaneous other vaccine.

In 2010 the number of reports was in line with other recent years, but less than 2009 with considerable public anxiety about the HPV and pandemic flu campaigns. Also the number of reported local reactions after the 4-years booster was less in 2010, although still high. The safety surveillance system has proven again to be very signal sensitive and the high quality of reports has supplied meaningful data useful for education, information and advice to providers and parents.

The 1380 reports should be balanced against the large number of vaccines administered; more than 1.3 million vaccinees received over 7 million vaccine components in 2010. The risk balance strongly favours the continuation of the vaccination programme.
Samenvatting


In 2010, net als eerder, werden de meeste meldingen telefonisch gedaan (84%), waarbij de mogelijkheid bestond om verduidelijking te vragen en te geven, naast overleg en advies. De meerderheid van de meldingen kwam van artsen en verpleegkundigen in de jeugdgezondheidszorg (81%). Aanvullende informatie werd verkregen van ouders, huisartsen en ziekenhuis specialisten in 85% van de meldingen. Het aandeel van meldingen met slechts gegevens van een enkele bron is over de jaren verminderd van 50% tot 10-15% vanaf 2004. Alle meldingen worden na validatie en aanvulling beoordeeld op diagnose en oorzakelijk verband met de vaccinatie. De in dit rapport opgenomen gegevens zijn gebaseerd op de door het RIVM gestelde (werk)diagnoses aan de hand van casus definities en criteria voor causaliteit.

Bij het RIVM werden 1380 meldingen van vermoede bijwerkingen gedaan, betreffende 1260 kinderen. In 2010 zijn 800.000 kinderen gevaccineerd, in het totaal ruim 1,3 miljoen keer met een of meerdere vaccins. Bij elkaarm betrof dat meer dan 7 miljoen vaccincomponenten. Dat betekent een globale meldgraad van 158 gemelde kinderen per 100.000 entelingen en 104 meldingen per 100.000 prikmomenten. Per vaccin en vaccindosis zijn er grote verschillen en de hoogste meldgraad geldt de zuigelingen. Van de 1380 meldingen waren er slechts 2 niet te beoordelen door het ontbreken van essentiële informatie. Dit betroffen in beide gevallen milde verschijnselen. Van de resterende 1378 meldingen werden er 1082 (79%) als bijwerking beschouwd met een mogelijk, waarschijnlijk of zeker oorzakelijk verband met de vaccinatie. Van de overige 296 meldingen (21%) berustten de verschijnselen op een toevallige samenloop en niet op een bijwerking. Dit is vergelijkbaar met eerdere jaren.

739 meldingen (54%) zijn als zogenaamde ‘minor’ lokale of algemene ziektebeelden geclassificeerd, waarvan er 540 (73%) een mogelijk oorzakelijk verband hadden. Zogenaamde ‘major’ ziektebeelden werden 641 maal gerapporteerd, waarvan 542 (85%) met een mogelijk oorzakelijk verband. Deze major-meldingen omvatten de rubrieken collaps, stuipen, verkleurde benen, ontroostbaar langdurig krijsen en diverse ziektebeelden gegroepeerd onder algemene major-ziekten. Hieronder vallen ook de gemelde sterfgevallen en extreme lokale reacties (106) of eventuele ernstige huidverschijnselen (3).

Verkleurde benen werd 98 keer gemeld met oorzakelijk verband in 96 van de gemelde gevallen. Collaps reacties zijn bij 91 kinderen gerapporteerd, waarvan er 9 ongerelateerd waren. Alle 4 breath-holding spells (achterademhuiien of weghuilen), werden als bijwerking beschouwd. Flauwvallen (69), bij oudere kinderen, was slechts in 1 kind ongerelateerd. Van de 57 convulsies gingen er 49 gepaard met koorts, vooral optredend in de kinderen van rond 1 jaar oud. 41 convulsies waren mogelijk veroorzaakt door de (koorts van de) vaccinatie. Atypische aanvallen (24) hadden een mogelijk oorzakelijk verband in 13 meldingen. Epilepsie was in alle 4 gevallen niet door de vaccinatie
veroorzaakt of uitgelokt. Lang ontroostbaar huilen (meer dan 3 uur achtereen) werd 53 keer gemeld en op 2 na als bijwerking beschouwd.

In de ‘ziek-major’ categorie (100) werden 49 kinderen gerubriceerd met als hoofdverschijnsel zeer hoge koorts van 40,5 °C of meer, waarvan er 36 als mogelijke bijwerking werden geduid. Dit gold ook voor 2 kinderen met sterke ondertemperatuur zonder eerder opgemerkte koorts. Daarnaast waren er nog 6 kinderen met zeer hoge koorts, die tevens uitslag hadden ongeveer een week na de BMR-vaccinatie en die als ‘vaccinitis’ zijn geclassificeerd. Van de overige 43 ziek-major meldingen werden er 9 als bijwerking beschouwd (Idiopathische Thrombocytopenische Purpura (ITP)-4, apneu/saturatiedaling-2, migraine-1, artritis-1 en indirect mogelijk osteomyelitis-1).

3 lokale abcessen werden gemeld, waarvan 2 na BCG-vaccinatie (Bacille Calmette Guérin). In 2010 werden 5 sterfgevallen gemeld; alle hadden, na grondige beoordeling geen relatie met de vaccinaties. In 3 kinderen werd een obductie gedaan. De doodsoorzaak was complicaties van infectie in 3 kinderen en in 2 waarschijnlijk ontregeling van een stofwisselingsziekte. In geen van de kinderen heeft de vaccinatie een rol gespeeld in verergering van de ziekte of een te late diagnose.

Het frequentst (651) betroffen de meldingen de zuigelingen vaccinaties met DKTP-Hib (difterie, kinkhoest, tetanus, polio, *Haemophilus influenzae* type b), die in 97% tegelijk met Pneu (7-valent geconjugeerd pneumokokkenvaccin) werd gegeven. In 19% (124) werd tevens Hepatitis-B vaccin gegeven. De revaccinatie met DKTP op 4 jaar leverde 305 meldingen, in 8 gevallen samen met andere toegediende vaccins. BMR1 en MenC (Bof, Mazelen, Rodehond en meningokokken C) waren betrokken bij 195 meldingen, waarvan 13 keer apart toegediend (of BMR of MenC); 2 kinderen kregen tevens een ander vaccin. De revaccinaties op 9-jarige leeftijd met DTP en BMR gaven aanleiding tot 82 meldingen (waarvan 5x alleen DTP). 129 meldingen betroffen HPV-vaccin (humaan papilloma virus), eenmaal met tegelijk een ander vaccin.

Het aantal meldingen in 2010 was vergelijkbaar met andere jaren, hoewel minder dan in 2009. Toen vernoorzaakten 2 grote vaccinatiecampagnes aanmerkelijke publieke onrust, eerst voor HPV en later dat jaar voor pandemische griep. Dat genereerde veel vragen en ook meldingen. Een ander verschil is het lagere aantal heftige lokale reacties na de boostervaccinatie bij de kleuters, hoewel het aantal nog steeds hoog was.

Het gestimuleerde veiligheidsbewakingssysteem heeft ook dit jaar weer aangetoond zeer signaalgevoelig te zijn en de hoge kwaliteit van de gegevens kan een bijdrage leveren aan de voorlichting, begeleiding en advisering van zowel de beroepsbeoefenaren als de ouders. Het totale aantal van 1380 meldingen moet in relatie gezien worden met de grote aantallen gevaccineerde kinderen, prikmomenten en toegediende vaccins. De grote gezondheidswinst van het vaccinatieprogramma weegt ruimschoots op tegen het nadeel van de bijwerkingen.
1 Introduction

Identification, registration and assessment of adverse events following drug-use are important aspects of post marketing surveillance (PMS). Safety surveillance is even more important in the programmatic use of preventive interventions, especially when children are involved. In the Netherlands, the National Institute for Public Health and the Environment (RIVM) had the task to monitor adverse events following immunisation (AEFI) under the Netherlands Vaccination Programme (RVP). This programme started in 1957 with adoption of a passive safety surveillance system in 1962.

Since 1994, the RIVM reports annually on adverse events, based on the year of notification. The present report contains a detailed description of the procedures for soliciting notifications, verification of symptoms, diagnosis according to case definitions, and causality assessment for 2010. It also includes a description of the characteristics of the Netherlands Vaccination Programme and the embedding in the Child Health Care System (JGZ). The annual reports are not the primary target but the result of the aggregated analysis of all reported AEFI, with the aim to find signals and follow trends.

In the present report, we will go into the number of reports and the different aspects of the nature of the reported adverse events in 2010 and compare them with previous years. In 2010, the programme was similar to 2009, although different manufacturers supplied different vaccines. In addition, HPV was included for 13 year old girls in a 3-dose schedule after the catch up campaign of 2009 for cohorts 1993-1996.

Reports have been carefully monitored for unexpected, unknown, new severe or particular adverse events and to changes in trend and severity. The headlines of this 17th RIVM report on adverse events are also issued in Dutch. The report and the Dutch summary and aggregated tables will be posted on the RVP website, www.rvp.nl.

In 2008, the political decision has been made to outplace the safety surveillance of the RVP to Lareb (Netherlands Pharmacovigilance Centre 'Lareb'). Since January 2011, this has been implemented, with the registration of adverse events under the RVP at Lareb.

This annual report will thus be the last in the series. Therefore, it will also contain an overview of important and remarkable observations on adverse events over the years. In addition, some results from specific systematic studies on reports will be discussed.
2 The Netherlands Vaccination Programme

In the Netherlands, mass vaccination of children started in 1952, with institution of the Netherlands Vaccination Programme (RVP) in 1957. From the start, all vaccinations were free of charge and have never been mandatory. All vaccinations are registered on individual basis; first as method for remuneration of the provider and since around 1970 as vaccination register. For the current schedule, see Box 1.

2.1 Vaccines, Schedule and Registration

At first DT (against diphtheria and tetanus) with or without pertussis vaccine was offered to all post WWII cohorts. In 1957, a catch up campaign was held for polio with IPV (inactivated polio vaccine, except for epidemic area where oral polio vaccine-OPV was used). Since 1962, DT-IPV was offered to all children of 4 years and 9 years and combined DTP-IPV in a 4-dose infant schedule (3, 4, 5, 11 months). 1,2,3,4,5

In 1993, simultaneous vaccination against Haemophilus influenzae type B (Hib) was added to the infant schedule (combined vaccine since March 2003). In 1999, the accelerated infant schedule was adopted, with start at 2 months. 6 In 2005, we switched from whole-cell pertussis to acellular pertussis (aP) vaccine for infants. 7 For 4-year-olds, aP was already added in 2002 (for birth cohorts 1998 and after) to the booster DT-IPV, first as single simultaneous vaccine and gradually as combined vaccine in 2006.

Hepatitis B vaccine (HepB) was offered to infants of HBsAg positive mothers in a 4-dose schedule since 1989, simultaneously with DTP-IPV(+Hib), after HBIg administration at birth. 8 In March 2003, this 4-dose HepB schedule was replaced by a 3-dose schedule with a switch from adult to infant formulation (2, 4, 11 months). At that time, another HepB risk group was added with infants of parent(s) from high or middle HepB endemic areas in the world. 9

Meningococcal C vaccine (MenC) was introduced in 2002 for children 14 months of age, simultaneously with MMR. A catch up campaign for MenC targeted the 1-18 year-olds. 10

Rubella has been offered to 11 year old girls since 1974. Measles vaccine was introduced for 14m old children (from birth cohort 1975 onward). Transition to MMR was in 1987 (from July onwards) in a 2-dose schedule at 14 months and 9 years. This replaced the Rubella vaccination for girls only. For a few years, catch up MMR was offered with the booster DT-IPV at 4 years.

Conjugated pneumococcal vaccine (Pneu) was introduced in 2006 (for those born from April 2006 onward) in the 4-dose infant schedule; for the defined HepB risk group children DTP-IPV-HepB hexavalent vaccine became available and thus for HepB a return to a 4-dose schedule.

A HPV (human papilloma virus) catch up campaign was held in 2009, for girls of cohorts 1993-1996 in a 3-dose schedule. Because of the pandemic flu campaign, vaccination of the 1997 birth cohort was forwarded to spring 2010. 11

No further changes in the schedule for 2010 occurred, apart from the introduction of the postponed HPV vaccination for 12-13 year old girls. In 2011, 10-valent pneumococcal vaccine will replace the 7-valent vaccine (for infants born from March 2011 onward) and universal HepB vaccination for infants born from August 2011 onward will be introduced with hexavalent combination vaccine. The age limit for eligibility will be raised to 18 years inclusive. 12 Until then the age limit is 13 years, with restricted supply of Hib and Pneu up till 2 years. The schedule for 2010 is given in Box 1. (See also Appendix 1 for product characteristics)
Box 1  Schedule of the Netherlands Vaccination Programme in 2010

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>birth</td>
<td>HepB0</td>
</tr>
<tr>
<td>2 months</td>
<td>DTP-IPV-Hib1(-HepB) + Pneu 1</td>
</tr>
<tr>
<td>3 months</td>
<td>DTP-IPV-Hib2(-HepB) + Pneu 2</td>
</tr>
<tr>
<td>4 months</td>
<td>DTP-IPV-Hib3(-HepB) + Pneu 3</td>
</tr>
<tr>
<td>11 months</td>
<td>DTP-IPV-Hib4(-HepB) + Pneu 4</td>
</tr>
<tr>
<td>14 months</td>
<td>MMR1 + MenC</td>
</tr>
<tr>
<td>4 years</td>
<td>DTP-IPV5</td>
</tr>
<tr>
<td>9 years</td>
<td>DT-IPV6 + MMR2</td>
</tr>
<tr>
<td>12-13 years</td>
<td>HPV dose 1,2,3 girls only</td>
</tr>
</tbody>
</table>

* = for children born from HepB carrier mothers
b = for extended risk group of infants with parent(s) from middle of high endemic HepB countries.

Vaccines for the RVP are supplied by the Netherlands Vaccine Institute (NVI) and are kept in depot at a regional level of the Regional Coordination of Programmes (RCP). RCP is responsible for further distribution to providers and for implementation and monitoring cold chain procedures. The Medical District Consultant (MA) for RCP follows and promotes programme adherence.

The National Vaccination Register (Praeventis) has name, sex, address and birth date of all children up till 18 years (since the introduction of HPV vaccination in 2009, before up till 13 years). The database is linked with the municipal population register and is updated regularly or on line, for birth, death and migration. All administered vaccinations are entered in the database on individual level with specifics of product and lot numbers. For older birth cohorts information is available but not updated anymore. Summarised product characteristics of all used vaccines in 2010, are listed in Appendix 1 and full documents at www.cbg-meb.nl.

2.2  Child Health Care System

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

Up till 4 years of age (preschool) children attend the Child Health Clinic (CB) regularly. At school entry, the Municipal Health Service (GGD) takes over. The RVP is fully embedded in the Child Health Care system (JGZ) and vaccinations are given during the routine visits. Good professional standards include asking explicitly after adverse events following immunisation (AEFI) at the next visit and before administration of the next dose. The 4-year booster DTP-IPV is usually given at the last CB visit, before school entrance. Booster vaccination with DT-IPV+MMR at 9 years of age is organised in mass vaccination setting with a possibility of individual catch up. The Municipal Health Care provides HPV vaccination in mass vaccination settings as well, since HPV was added to the programme in 2009.

Attendance of Child Health Clinics is very high, up to 99% and vaccination coverage for the primary series DTP-IPV-Hib is over 97% with slightly lower coverage for MMR. Accurate numbers on birth cohort 2009 and 2010 have not been released yet.

2.3  Safety Surveillance

The safety surveillance of the RVP has been an acknowledged task of the National Institute for Public Health and Environment (RIVM); this is performed by the Centre for Infectious Disease Control Netherlands (CIb), independently from vaccine manufacturers.
Requirements for post marketing surveillance (PMS) of adverse events have been stipulated in Dutch and European guidelines and legislation. The World Health Organization (WHO) advises on monitoring of adverse events following immunisations (AEFI) against the target diseases of the Expanded Programme on Immunization (EPI) and on implementation of safety surveillance in the monitoring of vaccination programmes.  

The WHO keeps a register of adverse reactions as part of the global drug-monitoring programme. Currently there are several international projects to achieve a better quality of safety surveillance and to establish a register specifically for vaccines and vaccination programmes.

Close evaluation of the safety of vaccines differs from that of other pharmaceutical products (drugs) in quite a few aspects and needs its own tools and methods. It 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. Not only true side effects but also events with only temporal association with vaccination may jeopardise the uptake of the vaccination programme. This has been exemplified in Sweden, in the United Kingdom and in Japan, in the seventies and eigthies of the last century. 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 sequels of pertussis infection. In addition, recently concerns about safety rather than actual causal associations caused cessation of the hepatitis B programme in France. Even at this moment, the uptake of MMR in the United Kingdom and the Republic of Ireland is very much under pressure because of unfounded allegations about the association of the vaccine with autism and inflammatory bowel disease.

Subsequent (local) measles epidemics have occurred and are occurring as we speak, in Europe.

In the Netherlands, the basis for the safety surveillance of the RVP is an enhanced passive reporting system. Professionals ask for consultation and advice on vaccination matters like schedules, contra-indications, precautions and adverse events. Reporting can be done by telephone, regular mail, fax or email. Since 2009, a web based report form has been added to the other reporting routes. See for a detailed description on procedures chapter 3. The annually distributed vaccination programme (Appendix 2) encourages health care providers to report adverse events to RIVM.

Apart from the low threshold reporting and availability with personal communication, RIVM promotes reporting through information, education and publications. Feedback to the reporter of adverse events (AE) and other involved professionals has been an important tool in keeping the reporting rate at high levels.

A summarisation of the aggregated analysis of all reported adverse events is published annually by RIVM. Signals may lead to specific follow-up and systematic study of selected adverse events. The aggregated analysis and annual reports support a 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. The annual reports may also serve for the purpose of public accountability for the safety of the programme.
3 Materials and methods

3.1 Post Vaccination Events

Adverse events following immunisations (AEFI) do not necessarily have causal relation with vaccination. Some have temporal association only and are in fact merely coincidental.\textsuperscript{27,28} 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; for live vaccines, this risk window is six weeks. Some disease entities have a longer risk period. Following are some definitions used in this report:

- **Vaccine**: immuno-biologic product for active immunisation against infectious diseases.
- **Vaccination**: all activities necessary for vaccine administration.
- **Post vaccination event or adverse events following immunisation (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 (AR)**: adverse event with presumed, supposed or assessed causal relation with vaccination.

Adverse events are thus divided in coincidental events and genuine side effects (Box 2). Side effects are further subdivided in vaccine or vaccination intrinsic reactions, vaccine or vaccination potentiated events, and side effects through programmatic errors.\textsuperscript{50,51,52,53}

### Box 2 Origin / subdivision of adverse events by mechanism

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine or vaccination intrinsic reactions</td>
<td>are caused by vaccine constituents or by vaccination procedures; i.e. fever, local inflammation and crying.</td>
</tr>
<tr>
<td>Vaccine or vaccination potentiated events</td>
<td>are brought about in children with a special predisposition or risk factor; for instance, febrile convulsions.</td>
</tr>
<tr>
<td>Programmatic errors</td>
<td>are due to faulty procedures; for example the use of non-sterile materials; loss of effectiveness due to faulty procedures may also be seen as adverse event.</td>
</tr>
<tr>
<td>Chance occurrences or coincidental events</td>
<td>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.</td>
</tr>
</tbody>
</table>

3.2 Reporting Criteria

Any severe event, irrespective of assumed causality and medical intervention, should be reported. Furthermore, peculiar, uncommon or unexpected events and events leading to apprehension in parents and providers or to adverse publicity are also reportable (Box 3)

### Box 3 Reporting criteria for AEFI under the Netherlands Vaccination Programme

- Serious events;
- Uncommon events;
- Symptoms affecting subsequent vaccinations;
- Symptoms leading to public anxiety or concern;

irrespective of causal relation
Events resulting in deferral or cessation of further vaccinations are considered as serious and therefore should be reported as well (Box 3). Vaccine failures may result from programmatic errors and professionals are therefore invited to report these also.

### 3.3 Notification and Single, Compound or Multiple Reports

All incoming information on AEFI under the RVP, whether intended reports or requests for consultation about cases, are regarded as notifications. In this sense, also events that come from medical journals or lay press may be taken in if the reporting criteria apply (Box 3). The same may apply for events from active studies. All notifications are recorded on individual level. For analysis, we take into account all information on each notification and register all symptoms reported. For numbers strict rules apply as stipulated below. This is to assure meaningful figures, allowing follow-up of trends and realistic comparisons. Low-level terms are registered none the less, and may be used in screening procedures and signal detection, but we try to avoid blowing up of numbers, which only may reflect the level of detail in reports. Symptoms are used for application in event case definitions and are usually not the major unit in summarised annual reports. Thus, in the summarisation for the annual report, notifications are booked under the most important (working) diagnosis and not under each symptom separately. Some notifications lead to compound reports with more than one noteworthy event that are not interrelated. In addition, a notification may cover more than one vaccination date but this only leads to multiple reports if strict criteria are fulfilled. Below the subdivision of notifications in single, multiple and compound reports is further clarified (Box 4).

**Box 4 Subdivision of notifications of adverse events following vaccination**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single reports</td>
<td>concern one vaccination date;</td>
</tr>
<tr>
<td></td>
<td>have only minor symptoms and/or one distinct severe event.</td>
</tr>
<tr>
<td>Compound reports</td>
<td>concern one vaccination date;</td>
</tr>
<tr>
<td></td>
<td>have more than one distinct severe event.</td>
</tr>
<tr>
<td>Multiple reports</td>
<td>concern more than one vaccination date;</td>
</tr>
<tr>
<td></td>
<td>have one or more distinct severe event following each date or are notified</td>
</tr>
<tr>
<td></td>
<td>separately for each date.</td>
</tr>
<tr>
<td>Cluster reports</td>
<td>group of notifications on one vaccination date and/or one set of vaccines</td>
</tr>
<tr>
<td></td>
<td>or badges or one age group or one provider or area.</td>
</tr>
</tbody>
</table>

Most notifications concern events following just 1 vaccination date. These are filed as single reports, under the most prominent event. For example, (high) fever will be the working diagnosis and the moderate local reaction is not booked out as separate event. In addition, persistent screaming in an infant that cried 4 hours on end will be the leading event and not the 39.2 °C fever later that night, which is not counted as separate event.

Compound report classification follows, if the notification concerns more than one distinct event with severe or peculiar symptoms. The events should be without interrelation, i.e. discoloured legs with the child crying for 3 hours or more, is only booked under discoloured legs since we regard the vehement crying as part of this specific event. Likewise, fever of ≥40.5 °C in a child with a convulsion, is booked as febrile convulsion and not under very high fever also.

Multiple reports follow, if simultaneous notification is about severe or peculiar symptoms following different vaccination dates, each date is booked separately in the relevant event categories. However, if events consist of only minor local or systemic symptoms this results in a single report and the event is classified under the most appropriate vaccination date; this may be the vaccination with the most severe event or if similar event severity, the last vaccination. Time spaced notifications on different vaccinations in the same child, result in distinct reports irrespective of nature and severity of symptoms and are therefore multiple reports. Events after previous or subsequent vaccinations, that become known in
the process of verification, complementation or follow-up of a case, are generally not listed as separate events. Only, if the events are major or of special interest, this results in multiple reports. The same applies to experiences of adverse events in siblings, when talking to parents.

In case of cluster notifications, special procedures apply, because of the potential of signal/hazard detection. If assessed as non-important, minor symptoms or unrelated minor events, cluster notifications are booked as a single report. In case of severe events, the original cluster notification will be booked as separate reports after follow-up. Thus, the breakdown of the cluster will result in several single, multiple or compound reports. During annus, we continually keep an open eye for unexpected clustering of specific events in time, place, and type of vaccine or lot numbers.

3.4 Reporters and Information Sources
The first person to notify RIVM about an adverse event is the reporter. All others contacted are ‘informers’.

3.5 Additional Information
In the first notifying telephone call with the reporter, we try to obtain all necessary data on vaccines, symptoms, circumstances and medical history. We also discuss the procedures and proceedings. In addition, preliminary assessment is discussed and advice given on subsequent vaccinations. A physician reviews all notifications on a daily basis. The data are verified and the need for additional information is determined. As is often the case, apprehension, conflicting or missing information, make it necessary to take a full history from the parents with a detailed description of the adverse event and circumstances. In addition, the involved general practitioner (GP) or hospital is contacted to verify or complete symptoms in case of severe and complex events. Dates and lot numbers are supplemented and validated from the vaccination register.

3.6 Working Diagnosis and Event Categories
After verification and completion of data, a diagnosis is made. If symptoms do not fulfil the criteria for a specific diagnosis, a working diagnosis is made, based on the most important symptoms. In addition, 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 applied for the most common adverse events, and for other diagnoses current medical standards are used. 54,55

For the annual report, all reports are reassessed with subsequent aggregated analysis. The (working) diagnoses are classified under one of ten different event categories clarified below. Some categories are subdivided in minor and major according to the severity of symptoms. Major is not the same as medically severe or the regulatory use of serious, but this group does contain the severe events. Definitions for Serious Adverse Events (SAE) by European Medicines Agency (EMA) and International Conference on Harmonisation (ICH) differ from the criteria for major in this report. Below, the 10 different event categories are listed and described (Box 5).

- **Local (inflammatory) symptoms**
  These consist of symptoms at or near the injection site. 56,57,58 Events are booked here if concomitant systemic symptoms do not prevail. Events are booked as minor in case the (atypical) symptoms are limited in size and duration. Major events are extensive and/or prolonged and include events like abscess or erysipelas.

- **General illness**
  This category includes all events that cannot be categorised elsewhere as a kind of repository. Fever associated with convulsions or as part of another specific event, is
not listed separately. Crying as part of discoloured legs syndrome, is not booked separately. Symptoms like crying < 3 hours, fever <40.5°C, irritability, pallor, feeding and sleeping problems, mild infections, et cetera are booked as minor events. Major events include very high fever $\geq 40.5 \text{ ºC}$, autism, diabetes, ITP, severe infections, et cetera. 59,60,61

- **Persistent screaming**
  This major event is defined as (sudden) screaming, non-consolable and lasting for three hours or more. Persistent screaming as part of discoloured legs syndrome is not booked here separately. 62

- **General skin symptoms**
  Symptoms booked here are not part of general (rash) illness and not restricted to the injection site. Subdivision in minor and major, is made according to severity. 63

- **Discoloured legs**
  Events in this category are classified as major, and defined as even or patchy discoloration of the leg(s) and/or leg petechiae, with or without swelling. Extensive local reactions are not included. 64

- **Faints**
  Symptoms listed here are not explicable as post-ictal state or part of another disease entity. Three different diagnoses are included, all considered major:
  - Collapse is sudden pallor, loss of muscle tone and of responsiveness (HHE).65
  - Breath-holding-spell (BHS) is fierce crying, followed by a halt in breathing, with no pallor/cyanosis or loss of consciousness or for just a short period.
  - Fainting is sudden onset of pallor, with limpeness and accompanied by vasomotor symptoms, occurring in older children.

- **Fits**
  Three different diagnoses are included in this category, all considered major:
  - Convulsions are fits caused by abnormal or excessive neuronal brain activity with disturbed consciousness and abnormal movement and muscle tone. Convulsions/seizures are divided in non-febrile and febrile convulsions, and include all episodes with tonic and/or clonic muscle spasms and loss of consciousness. Simple febrile seizures last $\leq 15$ minutes. Complex febrile seizures last $>15$ minutes or recur within 24 hours or are asymmetrical. 66
  - Epilepsy is a chronic neurological illness with recurrent seizures, not being febrile convulsions. Only booked are definite epileptic fits or determined epilepsy.
  - Atypical attack is a paroxysmal occurrence, not fully meeting criteria for collapse or convulsion and not consistent with any other diagnosis.

- **Encephalitis /encephalopathy**
  Events booked here are considered major. A child <24 months with encephalopathy has loss of consciousness for $\geq 24$ hours. Children >24 months have at least two out of three criteria: change in mental state, decrease in consciousness, seizures. In case of encephalitis, symptoms are accompanied by inflammatory signs. Symptoms are not explained as post-ictal state or intoxication. This event is considered major. 67

- **Anaphylactic shock**
  This event consists of circulatory insufficiency with hypotension and life threatening hypo perfusion of vital organs with or without laryngeal oedema or bronchospasm. These major events must be in close temporal relation with the intake of an allergen and type I allergic mechanism is involved. This event is considered major. 68

- **Death**
  This category holds any death following immunisation. Preceding disease or underlying disorders are not booked separately. All events are considered major.
Box 5  Main event categories with subdivision according to severity

<table>
<thead>
<tr>
<th>Event Category</th>
<th>Subdivision</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>local reaction</td>
<td>minor</td>
<td>mild or moderate injection site inflammation or other local symptoms</td>
</tr>
<tr>
<td></td>
<td>major</td>
<td>severe or prolonged local symptoms or abscess</td>
</tr>
<tr>
<td>general illness</td>
<td>minor</td>
<td>mild or moderate general illness not included in the other specific categories</td>
</tr>
<tr>
<td></td>
<td>major</td>
<td>severe general illness, not included in the listed specific categories</td>
</tr>
<tr>
<td>persistent screaming</td>
<td>major</td>
<td>inconsolable crying for 3 or more hours on end</td>
</tr>
<tr>
<td>general skin symptoms</td>
<td>minor</td>
<td>skin symptoms not attributable to systemic disease or local reaction</td>
</tr>
<tr>
<td></td>
<td>major</td>
<td>severe skin symptoms or skin disease</td>
</tr>
<tr>
<td>discoloured legs</td>
<td>major</td>
<td>entity with even or patchy discoloration of legs not restricted to injection site and/or leg petechiae</td>
</tr>
<tr>
<td>faints</td>
<td>major</td>
<td>collapse with pallor or cyanosis, limpness and loss of consciousness; included are also fainting and breath holding spells</td>
</tr>
<tr>
<td>fits</td>
<td>major</td>
<td>seizures with or without fever, epilepsy or atypical attacks that could have been seizures</td>
</tr>
<tr>
<td>encephalitis/encephalopathy</td>
<td>major</td>
<td>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)</td>
</tr>
<tr>
<td>anaphylactic shock</td>
<td>major</td>
<td>life threatening circulatory insufficiency in close connection with intake of allergen, with or without laryngeal oedema or bronchospasm</td>
</tr>
<tr>
<td>death</td>
<td>major</td>
<td>any death following vaccination irrespective of cause</td>
</tr>
</tbody>
</table>

3.7  Causality Assessment

Once it has become clear what exactly happened and when, and predisposing factors and underlying disease and circumstances have been established, causality will be assessed. This requires adequate knowledge of epidemiology, child health, immunology, vaccinology, aetiology and differential diagnoses in paediatrics. The nature of the vaccine and its constituents determine which side effects it may have and after how much time they occur. For different (nature of) side effects different time limits/risk windows may be applied. Causal relation will then be appraised, based on a checklist, resulting in an indication of the probability/likelihood 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 (Box 6).

Box 6  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

Causality is classified under one of six different categories. If there appears to be reverse chronology and the event precedes the vaccination then the sixth category of no causal
relation is used. On rare occasions an event is also booked if the cause of the event is definitely proven to be another than the vaccination and it is not possible that the vaccination has attributed to the course of the illness. See for details of criteria Box 7.

**Box 7  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 |
| 6-No | The event precedes the vaccination or there is a definite other cause established without any (possible) attribution of the vaccination |

If a certain, probable or possible causal relation is established, the event is classified as adverse reaction or side effect. If causal relation is considered (highly) improbable, the event is considered coincidental or chance occurrence. In this annual report, this category also includes events without any causal relation with the vaccination.

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.

### 3.8 Recording, Filing, Feedback and Follow-up

Symptoms, (working) diagnosis, event category and assessed causal relation are recorded in the notification file together with all other information about the child, as medical history or discharge letters. All notifications are, after completion of assessment and feedback, coded on a structured form. If there is new follow-up information or a change in scientific knowledge, the case is reassessed and depending on the information, the original categorisation may be adapted.

In most cases, the probability of a causal relation is communicated during the first contact with the reporter. If the final assessment is different from the preliminary appraisal then this is communicated later on. Severe and otherwise important adverse events, as peculiarity or public unrest, may be put down in a formal written assessment and sent as feedback to the notifying physician and other involved medical professionals. This assures that everyone involved gets the same information and makes the assessment (procedure) transparent. This document is filed together with the other information on the case.

Follow-up from the reporter is requested routinely, if the subsequent vaccinations are followed by relevant adverse events. In case of uncertain diagnosis or non-resolved events, active follow-up is done by RIVM. By doing so, we also keep track of the confidence of the parents in the vaccinations. It enables us to estimate the risk of recurrence of some specific adverse events as well.

### 3.9 Annual Reports and Aggregated Analysis

The coded (digital) forms serve as data sheets for the annual reports. Coding follows strict criteria for case definitions and causality assessment. Grouped events are checked for maximum consistency. Conflicting information and complex events are discussed in
periodic case discussions and all coding is checked crosswise by a non-involved physician. Inconsistencies are discussed. Yearly we report on all incoming notifications.

3.10 Expert Panel

An expert panel re-evaluates a selection of reports. The basis for this is the formal written assessments by RIVM. If necessary, the panel has access to all information in the case file. Additional follow-up information may be requested from clinic, GP or hospital. The expert group consists of specialists on paediatrics, neurology, immunology, pharmacovigilance, microbiology and epidemiology and has been set up by RIVM to promote broad scientific discussion on reported adverse events.

3.11 Quality Assurance

Assessment of adverse events is directed by standard operating procedure. On regular basis internal inspections are done. Severe, complex, controversial and otherwise interesting events are discussed regularly in clinical conferences of the physicians of the RIVM. Coding and assessment is checked crosswise by a physician who is not involved in the case. Coding criteria are reviewed and discussed on a regular basis.

3.12 Medical Control Agency and Pharmacovigilance

RIVM and the Netherlands Pharmacovigilance Centre (LAREB) exchange all reported adverse events following immunisations under the RVP, thus allowing the Medical Evaluation Board of the Netherlands (CBG) to fulfil its obligations towards WHO and EMA.
4 Results

4.1 Number and Type of Reports

In 2010, RIVM received 1380 notifications of adverse events (Table 1). For the first time, this included reports on HPV vaccination, for girls born in 1997 (90) and some catch up vaccinations for older girls (39). Apart from the addition of HPV, there were no other changes in the schedule in the year under report (2010). The number of reports in 2010 is 16% less than in 2009 (statistically significant) and similar to 2008. Actually, since 2005 the number of reports has fluctuated considerably. There were several changes in the programme, with possible consequences on the number of reported adverse events. First, a decrease in reports followed the transition to acellular DTP-IPV-Hib in 2005. In 2006 we gradually switched to an infant vaccine formulation with five instead of three pertussis components and the heptavalent pneumococcal conjugate vaccine (PCV7) was added to the programme for children born from April onwards. At the same time, hexavalent DTP-IPV-Hib-HepB vaccine became available for risk groups, in order to reduce the number of injections.

In 2009, the RVP schedule did not change, but 2 large vaccination campaigns were held. In March 2009, a catch up campaign started for Human Papilloma Virus (HPV) vaccination for girls born in 1993-1996. In autumn 2009, all children aged 6m-5y were invited for vaccination against the pandemic influenza A (H1N1), also in mass vaccination setting (traditional risk groups were targeted earlier). The passive AE surveillance of the pandemic influenza vaccination campaign was separate from the regular routine RVP safety surveillance. Both campaigns evoked a lot of public and professional concern and RIVM received very many questions on contra-indications and previous adverse experiences with vaccination, resulting in more AE reports.

Table 1 Number of reported AEFI per year

<table>
<thead>
<tr>
<th>year of notification</th>
<th>number of reports</th>
<th>birth cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>712</td>
<td>195,611</td>
</tr>
<tr>
<td>1995</td>
<td>800</td>
<td>190,513</td>
</tr>
<tr>
<td>1996</td>
<td>732</td>
<td>189,521</td>
</tr>
<tr>
<td>1997</td>
<td>822</td>
<td>192,443</td>
</tr>
<tr>
<td>1998</td>
<td>1100</td>
<td>199,408</td>
</tr>
<tr>
<td>1999</td>
<td>1197</td>
<td>200,445</td>
</tr>
<tr>
<td>2000</td>
<td>1142</td>
<td>206,619</td>
</tr>
<tr>
<td>2001</td>
<td>1331</td>
<td>202,603</td>
</tr>
<tr>
<td>2002</td>
<td>1332</td>
<td>202,083</td>
</tr>
<tr>
<td>2003</td>
<td>1374</td>
<td>200,297</td>
</tr>
<tr>
<td>2004</td>
<td>2141</td>
<td>194,007</td>
</tr>
<tr>
<td>2005</td>
<td>1036</td>
<td>187,910</td>
</tr>
<tr>
<td>2006</td>
<td>1159</td>
<td>185,057</td>
</tr>
<tr>
<td>2007</td>
<td>995</td>
<td>181,336</td>
</tr>
<tr>
<td>2008</td>
<td>1290</td>
<td>184,634</td>
</tr>
<tr>
<td>2009</td>
<td>1647</td>
<td>184,824</td>
</tr>
<tr>
<td>2010</td>
<td>1380</td>
<td>183,366</td>
</tr>
</tbody>
</table>
For the period 1994 up till 2004 inclusive there were less frequent changes in the programme and use of only one brand of whole-cell DTP-IPV. We saw a gradual increase in the number of reported adverse events due to reduced underreporting, a stronger pertussis vaccine (1998), a change in the schedule with an earlier start (1999), and the introduction of new vaccines (MenC, and booster pertussis for 4-year-olds, in 2002). There was a sudden peak in numbers because of increased media attention (in 2004).

Information on birth cohort size is retrieved from www.statline.nl.

For all years listed, vaccination coverage has been over 95%. The overall reporting rate, standardised per 100,000 vaccinated infants, is shown in Figure 1. Since 1994, there is a trend towards a higher reporting rate, with an initial decrease after transition to acellular pertussis vaccines for the infant schedule. In the later years, the reporting rate was similar to the levels 1998-2003. See for the actual vaccination schedule in 2010, section 2.1.

![Figure 1 Reporting rate per 100,000 vaccinated infants for AEFI for 1994-2010, with moving average and trend line](image)

In 2010, the 1380 distinct adverse events (AE) concerned 1260 children. 58 Children had multiple reports, with 122 AE after 2 or more different vaccination dates. For 37 children, the report was compound with 2 or more distinct AE after one vaccination date (76 AE). For 7 children, the report was both compound and multiple, with 24 AE (Table 2).

Altogether, the reports of 2010 involve 1325 vaccination dates. Multiple and compound reports are listed under the respective adverse event categories (section 3.3).

### Table 2  Number and type of reported AEFI in 2004-2010

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>single</td>
<td>1158</td>
<td>1158</td>
<td>1404</td>
<td>1161</td>
<td>837</td>
<td>967</td>
<td>890</td>
<td>1756</td>
<td></td>
</tr>
<tr>
<td>multiple</td>
<td>58</td>
<td>122</td>
<td>151</td>
<td>60</td>
<td>107</td>
<td>116</td>
<td>99</td>
<td>280</td>
<td></td>
</tr>
<tr>
<td>compound</td>
<td>37</td>
<td>76</td>
<td>86</td>
<td>50</td>
<td>44</td>
<td>66</td>
<td>44</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>compound and multiple</td>
<td>7</td>
<td>24</td>
<td>6</td>
<td>19</td>
<td>7</td>
<td>10</td>
<td>3</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Total 2010</td>
<td>1260</td>
<td>1380</td>
<td>1647</td>
<td>1290</td>
<td>995</td>
<td>1159</td>
<td>1036</td>
<td>2141</td>
<td></td>
</tr>
</tbody>
</table>

* 25 children had also reports in previous years; these are not included
* 6 children with triple reports
* 2 children had triple reports

Over the years the proportion of single reports has diminished somewhat, with relatively more multiple and/or compound reports, at least up till 2004, going down from 98% in 1994 to 91% in 2010. Since 2003, the proportion of additional events because of multiple and compound reports, is more level and fluctuates around 7.5% with an outlier of 9.6% in 2004 (Figure 2). As explained in detail under methods, section 3.3, we have chosen to
list only the most important AE per reported child, unless it concerns more than one major event not being part of the same event entity. Notifications about different vaccination dates are only booked as separate reports if the events are either major or of special interest, unless specifically reported on separate occasions. Minor adverse events from spontaneous or requested follow-up, are only listed if of some special concern or reported explicitly as adverse reaction. We aim for trend analysis and sensitive signal detection without too much influence of increased detailed reporting of increased solicited follow-up. Adverse events reported by parents in tolerability studies, i.e. paper forms, on linked email questionnaires or internet forms, and are not included in this report. Needless to say that all reported symptoms are registered and are used in specific analyses.

Figure 2 Proportion of single event reports for 1994-2010 with proportion of additional events (multiple or compound)

The reports per month show variation, similar to previous years (Figure 3). The reports of 2004 and before are from the time that whole-cell pertussis was exclusively used for the infant schedule. The reports for 1994-2003 show a steady increase in average monthly levels with periods of (public) holidays apparent. In 2004, report numbers soared because of public/press, professional and political discussions about the safety and the effectiveness of the whole-cell pertussis vaccine.

Figure 3 Absolute numbers of reports per month for 1994-2010; reports for whole-cell pertussis DTP-IPV-Hib are in dashed lines

The monthly report line follows the intensity of the public debate in 2004. To a lesser extend this was also the case in 2009, spring and autumn, about the catch up campaign for HPV and the pandemic flu campaign, respectively, with discussion already starting at the end of 2008.
4.2 Reporters, Reporting Route, and Information Sources

4.2.1 Reporters

Child Health Care professionals accounted for 1112 reports (81%) in 2010. In 192 reports (13.9%), parents were the reporter. The proportion of parents as reporter increased gradually from 3.5% to 9% between 1994 and 2003 and since 2004, the range has been 9.7-12.7%. See Figures 5B and 6, for a breakdown over the different vaccine doses. The share of other reporters was more or less stable (Figure 4 and Table 3). Over the years, the share of paediatricians diminished somewhat, from the range of 4.2-8.4% to 2.7-4.5% (for 1994-2003 and 2004-2009 respectively).

The 2 events under ‘other’ were reports by a pharmacist and by a social service organisation. Eight reports came from the Netherlands Pharmacovigilance Centre-Lareb; these were filed under the indicated respective primary reporter categories. In one of these eight cases, we were not able to validate the reported information and/or secure additional or follow-up data.

Table 3 Source and route of reported AEFI in 2004-2010

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Child Health Care</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child health clinic</td>
<td>991</td>
<td>91.3%</td>
<td>1271</td>
<td>1010</td>
<td>777</td>
<td>894</td>
<td>775</td>
<td>1685</td>
</tr>
<tr>
<td>Municipal health service</td>
<td>107</td>
<td>27.1%</td>
<td>51</td>
<td>81</td>
<td>50</td>
<td>80</td>
<td>76</td>
<td>44</td>
</tr>
<tr>
<td>District Consultant</td>
<td>14</td>
<td>78.6%</td>
<td>28</td>
<td>9</td>
<td>18</td>
<td>8</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Paediatrician</td>
<td>47</td>
<td>85.1%</td>
<td>46</td>
<td>35</td>
<td>33</td>
<td>35</td>
<td>48</td>
<td>84</td>
</tr>
<tr>
<td>General Practitioner</td>
<td>27</td>
<td>88.9%</td>
<td>35</td>
<td>23</td>
<td>15</td>
<td>11</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>Parent</td>
<td>197</td>
<td>77.6%</td>
<td>206</td>
<td>125</td>
<td>98</td>
<td>121</td>
<td>102</td>
<td>271</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>100%</td>
<td>10</td>
<td>7</td>
<td>4</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1380</td>
<td>84.1%</td>
<td>1647</td>
<td>1290</td>
<td>995</td>
<td>1159</td>
<td>1036</td>
<td>2141</td>
</tr>
<tr>
<td>(% written reports)</td>
<td></td>
<td>(16)</td>
<td>(13.2)</td>
<td>(8.1)</td>
<td>(7.8)</td>
<td>(9.6)</td>
<td>(11.3)</td>
<td>(12.9)</td>
</tr>
</tbody>
</table>

4.2.2 Reporting Route

As in previous years the vast majority of reports (1159; 84%) reached us by telephone. In 2010 we received 221 (16%) written reports, including 74 electronic/digital reports, 62 reports by email and only one report by fax (Table 3 and Figures 4 and 5). The Municipal Health Service reported only in 27% by telephone, mainly for HPV vaccination.
The increase in written reports was mainly due to these HPV reports for which specific report forms were distributed in 2009 and 2010 to municipal health services. Both clinics and parents, used the digital reporting form introduced in 2009.

The proportion written reports was around 4-5% until 2002. This proportion increased somewhat since then, when report forms (2002), email (2002) and digital report forms (2009) became available. See Figures 5A and 5B.

![Figure 5A](image1.png) *Route of incoming written reports in AEFI for 1994-2010*

![Figure 5B](image2.png) *Reporters, routes, single information source in reported AEFI for 1994-2010*

Even if a report had been submitted in writing, personal consultation and advice was in most cases appreciated or sought by the reporter. Again, this year our experience was that the need for advice and not so much the necessity of reporting was the drive for notification in quite a few reports including some severe events.

Written notifications are more prevalent in the older age groups, i.e. the 9y-boosters and the HPV vaccination. The same applies for parental reporting. For the infant vaccinations, MMR and MenC, and the 4y-booster, the proportions are much lower, for both written reports and parental reports, as is shown in Figure 6.
4.2.3 Regional Distribution and Reporting Rates

Reports were not evenly spread over the regions. Historically, the standardisation of these regional rates per 1000 vaccinated infants (dose 3) is done according to coverage data from the RCP. Rates were calculated with vaccination coverage data from Praeventis, the centralised web based vaccination register. Since the regular summarised reports of coverage data do not contain information on timing of the vaccination, there will remain inevitably some inaccuracy in estimated rates per region.

The birth cohort increased from a little below 190,000 in 1996 to 206,619 in 2000. Subsequently the birth cohort decreased to 181,336 in 2007. Then again, an increase occurred to 184,634 and 184,824 in 2008 and 2009, respectively and for 2010, the birth cohort was 183,866.

The overall reporting rate was 7.9 per 1000 vaccinated infants (DTP-IPV-Hib3) in 2010 (Table 4). The 95% confidence intervals for the reporting rates in the different regions contained the country’s overall reporting rate in 10 of the 15 regions.

Since 1994, the reporting rate went up from 3.6 per 1000 vaccinated infants, gradually to 7.2 in 2003. In 2004, there was an exceptionally high reporting rate of 11.5, due to persistent adverse publicity. The range for 2005-2008 was 5.6-7.2 (DTP-IPV-Hib3). In 2009, the reporting rate was again higher probably because of the public concern raised by the 2 mass vaccination campaigns. The increase of reports after the booster dose, at 4 years of age, contributed also to the higher reporting rate in 2009.

The country’s reporting rate for major events is 3.5/1000, similar to 2009 and 2008. This year the variation between regions in reporting rates for major AE was not statistically significant.

The reporting rate per 1000 vaccinated infants for major adverse events in 2005-2008 fluctuated between 2.5 and 3.4 and from 2000-2003 between 3.1- 3.7 with as outlier 2004 with 6.1 major adverse events reported per 1000 infants. For 2008-2010, rates are an estimate of the true reporting rates, due to lack of detailed vaccination coverage data for these years and changes in the birth cohort. However, vaccination coverage is very stable and the size of cohorts in those years differs not much, with the fluctuation being within 2%. 14
Table 4  Regional distribution of AEFI reports in 2004-2010, per 1000 vaccinated infants\(^a\) with proportionate confidence interval for 2010\(^b\) (major adverse events).

<table>
<thead>
<tr>
<th>Region</th>
<th>2010 (major)</th>
<th>95% CI 2010 (major)</th>
<th>2009 (major)</th>
<th>2008 (major)</th>
<th>2007 (major)</th>
<th>2006 (major)</th>
<th>2005 (major)</th>
<th>2004 (major)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groningen</td>
<td>6.2 (4.0)</td>
<td>4.3-8.5 (2.6-5.9)</td>
<td>8.6 (4.3)</td>
<td>6.3 (3.4)</td>
<td>5.1 (2.4)</td>
<td>7.4 (3.8)</td>
<td>6.7 (2.5)</td>
<td>16.4 (9.8)</td>
</tr>
<tr>
<td>Friesland</td>
<td>9.1 (5.0)</td>
<td>7.1-11.6 (3.5-6.9)</td>
<td>8.4 (2.4)</td>
<td>6.9 (3.4)</td>
<td>4.3 (2.4)</td>
<td>5.9 (3.1)</td>
<td>5.1 (3.0)</td>
<td>13.1 (7.7)</td>
</tr>
<tr>
<td>Drenthe</td>
<td>4.4 (2.6)</td>
<td>2.8-6.6 (1.4-4.3)</td>
<td>8.7 (4.1)</td>
<td>3.3 (1.6)</td>
<td>2.6 (1.4)</td>
<td>5.4 (2.7)</td>
<td>5.3 (2.7)</td>
<td>12.6 (10.1)</td>
</tr>
<tr>
<td>Overijssel</td>
<td>7.7 (2.5)</td>
<td>6.3-9.4 (1.8-3.5)</td>
<td>11.6 (4.4)</td>
<td>8.3 (3.7)</td>
<td>6.3 (2.9)</td>
<td>7.0 (3.5)</td>
<td>4.2 (1.6)</td>
<td>11.2 (5.8)</td>
</tr>
<tr>
<td>Flevoland</td>
<td>9.7 (4.1)</td>
<td>7.2-12.7 (2-6.2)</td>
<td>10.2 (4.1)</td>
<td>7.6 (2.5)</td>
<td>4.9 (1.4)</td>
<td>6.1 (2.5)</td>
<td>8.7 (3.7)</td>
<td>16.3 (9.1)</td>
</tr>
<tr>
<td>Gelderland</td>
<td>7.4 (3.2)</td>
<td>6.6-9.0 (2.5-4.0)</td>
<td>9.6 (3.6)</td>
<td>6.6 (2.5)</td>
<td>6.0 (2.6)</td>
<td>6.0 (2.9)</td>
<td>5.8 (2.4)</td>
<td>10.8 (5.8)</td>
</tr>
<tr>
<td>Utrecht</td>
<td>9.4 (3.6)</td>
<td>7.9-11.0 (2.7-4.6)</td>
<td>11.1 (4.9)</td>
<td>9.9 (5.7)</td>
<td>7.3 (3.2)</td>
<td>8.6 (5.5)</td>
<td>8.1 (4.6)</td>
<td>8.1 (4.9)</td>
</tr>
<tr>
<td>Noord-Holland(^c)</td>
<td>9.7 (3.9)</td>
<td>8.4-11.1 (3.1-4.9)</td>
<td>8.8 (3.2)</td>
<td>6.5 (2.4)</td>
<td>4.9 (1.8)</td>
<td>5.8 (3.2)</td>
<td>5.0 (2.5)</td>
<td>9.3 (5.2)</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>7.6 (4.3)</td>
<td>5.9-9.6 (3.1-5.9)</td>
<td>6.6 (2.4)</td>
<td>9.5 (4.3)</td>
<td>4.6 (1.8)</td>
<td>6.9 (3.6)</td>
<td>5.4 (2.1)</td>
<td>9.8 (4.1)</td>
</tr>
<tr>
<td>Zuid-Holland(^c)</td>
<td>7.5 (3.1)</td>
<td>6.5-8.6 (2.5-3.8)</td>
<td>9.9 (3.6)</td>
<td>7.2 (3.7)</td>
<td>5.9 (2.5)</td>
<td>6.6 (2.9)</td>
<td>5.2 (2.5)</td>
<td>11.6 (6.4)</td>
</tr>
<tr>
<td>Rotterdam</td>
<td>2.7 (2.1)</td>
<td>1.7-4.2 (1.2-3.5)</td>
<td>3.6 (1.4)</td>
<td>5.0 (2.3)</td>
<td>3.0 (1.4)</td>
<td>4.5 (2.0)</td>
<td>3.7 (1.9)</td>
<td>6.6 (4.7)</td>
</tr>
<tr>
<td>Den Haag</td>
<td>10.6 (4.9)</td>
<td>8.1-13.3 (3.3-6.9)</td>
<td>8.6 (3.4)</td>
<td>6.5 (3.3)</td>
<td>6.8 (3.6)</td>
<td>4.1 (1.5)</td>
<td>5.8 (1.9)</td>
<td>9.5 (5.8)</td>
</tr>
<tr>
<td>Zeeland</td>
<td>4.6 (3.2)</td>
<td>2.7-7.3 (1.7-5.5)</td>
<td>10.2 (6.1)</td>
<td>4.8 (2.8)</td>
<td>6.0 (2.6)</td>
<td>5.4 (2.8)</td>
<td>4.1 (1.6)</td>
<td>14.1 (10.7)</td>
</tr>
<tr>
<td>Noord-Brabant</td>
<td>7.1 (3.6)</td>
<td>6.1-8.2 (2.9-4.4)</td>
<td>8.8 (3.3)</td>
<td>7.9 (3.9)</td>
<td>6.9 (3.3)</td>
<td>7.1 (3.6)</td>
<td>6.8 (3.3)</td>
<td>14.5 (8.5)</td>
</tr>
<tr>
<td>Limburg</td>
<td>9.2 (4.2)</td>
<td>7.4-11.3 (3.0-5.7)</td>
<td>8.6 (4.1)</td>
<td>5.4 (2.7)</td>
<td>4.2 (2.4)</td>
<td>6.3 (2.7)</td>
<td>5.2 (2.9)</td>
<td>12.0 (6.8)</td>
</tr>
</tbody>
</table>

Range for regions:
- 2.7-10.6 (2.1-5.0)
- 3.6-11.6 (3.3-3.8)
- 3.3-9.5 (1.6-3.6)
- 2.6-7.3 (1.5-2.6)
- 4.1-7.4 (1.4-4.6)
- 3.7-8.7 (1.7-4.6)
- 6.6-16.4 (4.1-10.7)

The reporting rates for both minor and major adverse events over the years are consistent within and between regions. The outlier of 2004 behaves in a similar pattern and is therefore included in the mean for the 1994-2004 period. South is the region reporting the most, as is illustrated in Figure 7. East mimics the overall average, also for 2004.

---

\(^a\) for 2004 until 2006 included coverage data of the corresponding year from PraeEvents have been used; data of 2006 have been applied to 2007, 2008, 2009 and 2010 as well, because detailed definite numbers were not available yet.

\(^b\) Confidence limits not containing overall reporting rate in red

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

Figure 7 Reporting rate per 1000 vaccinated infants per region for 2010 compared with 1994-2004 and 2005-2009
For a breakdown of reporting rates per vaccine dose and per type of event, see under section 4.3.3 and the specific event categories under section 4.8.

4.2.4 Source of Additional Information

For all reports, we checked the date of vaccination, dose number, manufacturer and lot number of administered vaccines, with the entries in the National Vaccination Register. For a few reported AE we got this information, from the (hospital) pharmacist or the travel clinic if the vaccines were not administered by the child health care system. From the reporter we collected detailed information about the adverse event and underlying / pre-existent health issues of the vaccinee. We try to get an eyewitness account of the event from the parent if possible and supplement the data with information from GP or specialist if appropriate.

Table 5 Proportion of reports per reporting route and single information source

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Major AE in all Phone reports</td>
<td>54</td>
<td>54</td>
<td>56</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>Major AE in all Written Reports</td>
<td>55</td>
<td>60</td>
<td>65</td>
<td>53</td>
<td>41</td>
</tr>
<tr>
<td>1 source for all Minor AE</td>
<td>52</td>
<td>36</td>
<td>18</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>1 source for all Major AE</td>
<td>30</td>
<td>15</td>
<td>10</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>1 source for all Phone reports</td>
<td>40</td>
<td>24</td>
<td>11</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>1 source for all Written reports</td>
<td>44</td>
<td>35</td>
<td>28</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>1 source for Major Phone reports</td>
<td>30</td>
<td>14</td>
<td>7</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>1 source for Major Written reports</td>
<td>31</td>
<td>30</td>
<td>26</td>
<td>33</td>
<td>22</td>
</tr>
<tr>
<td>1 source for All reports</td>
<td>40</td>
<td>25</td>
<td>13</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

In 2010, 15% of reports had information only from the reporter. Over the years, the proportion of reports with information from a single source (solely the reporter) decreased from a little above 50% to 10-15% since 2004 (Figure 5B in section 4.2.2).

As shown in figure 8 and table 5, the proportion single information source reports went down for all types of reports, overall and for phone and written, but least of all for the written notifications (orange bold solid line); these written reports were for a higher proportion more severe (major) than the reports made by phone (orange fine solid line). These written major reports had a higher proportion of single information with the level remaining, a little above 30% (orange bold dashed line). However, representing 16% of all reports the number of written notifications remains relatively small.

A check on completeness of information of these written reports, over the last few years showed that their quality was actually poorer and more inaccurate. More reports were anonymous, contained faulty birth dates and wrong vaccination dates et cetera. To track down additional information took generally more effort and time and was often unsuccessful. Comparison is hampered because phone reports are complemented and clarified in the reporting phone call, a feature not possible in written reports. In the final report information and coding these reports were of less quality compared with the reports made by phone and a smaller proportion than in the phone reports had the highest level of certainty of the diagnosis (according to the Brighton Collaboration).

In 2010, we had information from others than the reporter in 85% of cases. A detailed account from the parents was received in 92%. The GP supplied information for 144 (10%) reported adverse events and from the hospital we received information in 227 (20%) cases. See for the breakdown of information sources per event category Table 8 in section 4.4.2.
Figure 8  Trends from 1996-2010 for the proportion of reports with only one information source per type of report.

The distribution of single source reports over the different vaccine doses is shown in Figure 9. The infant doses and the first MMR have the lowest proportion of single source reports and the dose at 9 years the highest. This age group has the largest proportion of written notifications as well as the largest proportion of parental reports. For the other doses, the pattern is more or less similar, with parental reports for infant doses up to 10% and for MMR up to 18% with the 4 years dose in between. Written notifications fluctuate around 10% for these doses. For HPV the single source proportion is 37% and 35% in 2009 and 2010 for all doses combined.

Figure 9  Proportion single source reports per vaccine dose 1996-2010 (HPV all doses)

4.3  Vaccines, Schedule, Age and Sex Distribution

4.3.1  Vaccines and Reports per Dose

In the current year, 96% of the notifications concerned recent vaccinations. Recent has been defined as a reporting lag of less than 365 days. This is in line with other years. Some of the 51 late reports arose from concerns about planned boosters or vaccination of younger siblings (5 times relating to imminent vaccination with or adverse experience after HPV or H1N1 vaccinations). AEFI described here, do not exclusively concern the RVP
schedule of the year under report (Table 6). Children may have received different vaccines because of immigration or for medical reasons. Some children, born in a specific calendar year, are not eligible to follow the specified programme, because introduction of new vaccines or changes in the programme not always start at January 1st or apply for a full birth cohort (see also section 2.1 for vaccines and schedule changes).

In Table 6, the scheduled and the actually administered vaccines are listed. For the third year in a row, reports following the DTP-IPV booster at 4 years of age are the most prevalent. See for more information on these 4y booster reports under section 4.7.1. This year for the first time HPV was included in the Netherlands Vaccination Programme, in a 3 dose schedule for 13 year old girls (cohort 1997). In addition, some HPV reports (39) concerned late doses in children vaccinated under the catch up HPV campaign (girls of cohorts 1993-1996). See for HPV section 4.7.2.

Of all infant doses, only one was DT-IPV, without pertussis, a late starter by parental choice. All other doses included the pertussis component; 77.8% received the regular DTP-IPV-Hib+Pneu and 19.2% (125) also HepB by hexavalent DTP-IPV-Hib-HepB. Only 2.9% had another combination of vaccines administered of which 7 were late reports, vaccinated according to the schedule at that time. 14 eligible children (2.2%) did not receive the scheduled Pneu, of which 2 also opted out of the Hib vaccine.

7 times MMR0 was administered for travel to measles endemic (or epidemic) areas, 3 times with simultaneous other vaccines. In 170 cases the scheduled MMR and MenC have been given, 8 times only MMR and once MMR with HepA, 3 times only MenC; another 4 times MMR was administered together with DPT-IPV and once with DT-IPV in a catch up schedule.

At the age of 4 years, out of the 313 reports, 6 concerned other vaccines than the scheduled booster (5 times MenC and once HepA). 15 reports had other vaccines simultaneously with the 4y DTP-IPV booster, mostly in a catch up schedule. See for more specifics on the 4y booster reports under section 4.7.1.

At 9 years of age, of the 84 reports, 77 reported children received the scheduled DT-IPV+MMR2, once with HepB. 3 children received DT-IPV, once with HepB and 1 only MMR. Another 3 children received non-scheduled vaccines (once influenza, once MenC and once HepB).

Since the additional HepB risk group has been added to the vaccination programme, the proportion infant reports with single HepB went up from 0.1-0.5% to 5% in 2003 when the additional risk group has been added. In 2004 and 2005 this proportion increased, to 9% and 7% respectively, mostly given with simultaneous DTP-IPV-Hib. In 2006, when the conjugated Pneumococcal vaccine was added to the schedule, we switched from the single HepB vaccine to the hexavalent vaccine to reduce the number of injections.

In 2006, the share of the AE reports after HepB in the infant schedule increased to 12% in 2006 and 2007, and further to 15% in 2008 with 14% in 2009. In 2010, the proportion of the hexavalent vaccine in the reported infant AE was 19%. This is a little higher than the proportion of infants vaccinated against HepB, which is 16-17% of all vaccinated infants (since 2003). For the last 5 years (since 2005), this was lower than the proportion of infants vaccinated. Also in 2005, we used one brand of pentavalent infant vaccine (with 3 pertussis components) for children not eligible for HepB and shifted gradually in the first months of 2006 to another brand (with 5 pertussis components). No conclusions can be drawn, without exact denominators from the vaccination register.

After the transition from whole-cell to acellular pertussis DTP-IPV-Hib, the number of reported adverse events after the infant doses fluctuates at a lower level. Before 2005, the proportion of infant dose reports was around 80% and after, the proportion decreased to around 60%, and following the increase in 4y-booster dose the proportion of reports
decreased further to around 50% (Figure 10). Mind that this is a relative distribution within the reports of vaccine doses involved. However, absolute numbers are influenced somewhat by changes in the size of the birth cohort and vaccination coverage.

Table 6  Scheduled and administered vaccines in reported AEFI in 2010

<table>
<thead>
<tr>
<th>vaccine</th>
<th>dtp-ipv</th>
<th>dt-ipv</th>
<th>mmr</th>
<th>mmr</th>
<th>dtp-ipv</th>
<th>mmr</th>
<th>dt-ipv</th>
<th>mmr</th>
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<th>mmr</th>
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</thead>
<tbody>
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<td>2010</td>
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</tbody>
</table>

- a once dtp-ipv + single hib vaccine
- b once dtp-ipv-hib + hepB single vaccine
- c once + menC
- d once dtp-ipv-hib + single aP by mistake and once dtp-ipv + single hib vaccine
- e once + bcg and once + bcg and mmr and 3 times primary dose late starters
- x 6 times primary dose in late starters
- f dtp1 as late starter
- g once + pneu
- h once + rabies vaccine and once + bcg
- i once + hepa
- j once without pneu
- k 4 times + mmr, once each + menC, influenza (pandemic) or hepB and 4 times dt-ipv + single aP
- l hepa
- m once + hepB
- n once + hepa and once dtp-ipv + mmr
- o once hepB and once influenza
- p 39 times late catch up of campaign and 90 in regular programme, once with hepB
- q 3 times bcg, 7 times seasonal influenza and 5 times pandemic influenza vaccine
- r all reports from hpv catch up campaign, the planned start of hpv under the vaccination programme has been postponed because of the pandemic influenza vaccination campaign
- s hpv not included in number of reports of 2009, reported separately in campaign surveillance
Figure 10  Relative frequencies of vaccine doses in AEFI reports for 1994-2010, without HPV

Figure 11A and 11B show the reporting rate per dose for 2010 compared with the 5 previous years combined and with the earlier periods combined in 2 blocks of 5 years, with 2004 separate as a clear outlier. Because accurate coverage data were not yet available for all cohorts concerned, we therefore used numbers for the actual birth cohort adjusted for the most recent coverage data per dose. Coverage rates per dose are very similar over the years so inaccuracies will only be minor. The increased rate at 4 years compared with the mean over 2005-2009 is more in perspective in figure 11B. For specifics on this 4y-booster dose, see section 4.7.1.

Figure 11A Reporting rate per dose per 100,000 vaccinated children for 1994-2010, with for HPV only first dose included and only 2009 and 2010

Figure 11B Reporting rate per dose per 100,000 vaccinees for 1994-2010 (HPV dose 1)
4.3.2 Age at Vaccination

The age at vaccination in reported AE reflects the schedule. Only very few reported children have an alternative schedule with late start or vaccines separated in time. Some follow a catch up schedule after immigration and some have had their subsequent vaccinations delayed because of an adverse event following the previous vaccination or an intercurrent illness. For 2010 the infant doses of DTP-IPV-Hib(-HepB) had some outliers in timing or age of the vaccinee (Table 7).

Table 7 Age according to schedule and in reported children

<table>
<thead>
<tr>
<th>Vaccine dose</th>
<th>Target age m/y (days)</th>
<th>Median in days (incl. outliers*)</th>
<th>Range in days (incl. outliers*)</th>
<th>N reports (n,% outliers*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant dose 1</td>
<td>2 months (61)</td>
<td>62 (62)</td>
<td>47-129 (-1143)</td>
<td>242 (8; 3.2%)</td>
</tr>
<tr>
<td>Infant dose 2</td>
<td>3 months (91)</td>
<td>98 (98)</td>
<td>62-292 (-458)</td>
<td>172 (4; 2.3%)</td>
</tr>
<tr>
<td>Infant dose 3</td>
<td>4 months (121)</td>
<td>132 (134)</td>
<td>109-293 (-1514)</td>
<td>98 (7; 6.7%)</td>
</tr>
<tr>
<td>Infant dose 4</td>
<td>11 months (334)</td>
<td>348</td>
<td>307-690</td>
<td>125 (0; 0%)</td>
</tr>
<tr>
<td>MMR 1</td>
<td>14 months (425)</td>
<td>437 (438)</td>
<td>180-663 (-1427)</td>
<td>183 (8; 3.7%)</td>
</tr>
<tr>
<td>4 yrs booster</td>
<td>4 years (1461)</td>
<td>1408</td>
<td>857-1748</td>
<td>296 (0; 0%)</td>
</tr>
<tr>
<td>9 yrs booster</td>
<td>9 years (3285)</td>
<td>3290</td>
<td>2089-4210</td>
<td>81 (0; 0%)</td>
</tr>
</tbody>
</table>

* outlier: age >6m for dose 2, >10m for dose 2-3 and >2y for dose 4 and MMR

For the infant doses, there were 19 late starters or catch up doses (2.9%); 5 were immigrants (asylum seekers, adoption, or other migrants) and 2 had an underlying illness that caused the delay. For 12 children the late start or late continuation of the schedule was more or less by parental choice. For the first dose of MMR (184 children), of which 7 times MMR0, 6 reported children (3.3%) had the vaccination after the age of 2 years (3 adopted or migrant children). In this respect, the reported children are therefore not much different from their peers. 

Remarkable is the lack of reports on the birth dose of HepB vaccine, included since 2003; only once we received such a report (2004).

Figure 12 Age distribution of reported children for infant doses and MMR1 for 1996-2010; in 1999 the accelerated schedule was adopted, starting the first dose at 2 months of age

Over the years, the median age at the first infant dose in reported children was 95 days up till 1999. After the accelerated schedule was adopted, the median age decreased in 1999 to 69 days and since then fluctuated between 65 or 64 days. This reflects the change in schedule. In 2008 and 2009, the median age for the first dose in reported children was 62 days, equal to 2010. The median age for the third dose was 166 or 167 days and went down to 156 days in 1999, thereafter fluctuating between 135 and 136 days up till 2004.
In 2005 and 2006, this was 138 days and since then 131, 134, 133 and 134 in 2007, 2008, 2009 and 2010 respectively (including a few outliers, with a late start or delayed continuation of the schedule). In Figure 12, the age distribution is illustrated, showing the consistency with the schedule over the years.

4.3.3 Sex Distribution

In the current year, 55% of the reported cases were male, with exemption of HPV reports, which by eligibility only covered girls. Of 3 events, the sex could not be determined – all in faints of schoolchildren, once because of cluster report.

![Figure 13 Proportion males in AEFI reports for 1994-2010](image)

Over the years, there has always been some excess of boys in the reports. As shown in Figure 13 the proportion of boys reported was 60% in 1994, diminished in the following 3 years, and was 54% until 2000. Since 2001, the male proportion fluctuated around 53% with considerable variation (range 51-54%). For 1994-2004 the average male proportion was 54% and for 2005-2010 53%. (In 2010, the proportion males in 0, 1, 2, 4 and 9 year old children was 51% in the Netherlands, [www.statline.nl](http://www.statline.nl))

![Figure 14 Proportion males per vaccine dose in 2010 and the 5 previous years, compared with the mean for 1996-2004](image)
Comparison of the sex distribution for the different vaccine doses over the last 6 years, shows that the male proportion per dose fluctuates around the average for the whole-cell period from 1996-2004. This also is illustrated in Figure 14. For 2010 the highest proportion males in the reports is registered for the 4- and 9-year-olds, both 60%. See for more details about the sex distribution for the different event categories under section 4.8.

4.4 Diagnoses, Severity, Information Sources and Medical Intervention

The diagnosis in reported adverse events is made, as much as possible according to standardised case definitions as is described in section 3.6. The reported diagnosis is always checked, and recoded if necessary. This assures homogeneous event categories and allows for trend analysis and systematic follow-up studies.

We use 10 different event categories, which harbour several diagnostic subgroups. Although we register all reported symptoms we try to avoid to list them as multiple events and categorise reported children under the most pronounced or severe diagnosis unless the notification concerns more than one non-related major event or event of special interest. In addition, minor events after previous or subsequent vaccinations that are mentioned/discussed, or come to our attention, in the follow-up of a reported AE are not listed, unless they are explicitly reported.

4.4.1 Diagnosis and Severity

Classification into disease groups or event categories is done after full assessment of the reported adverse event. As to be expected and consistent with previous years, the largest is the general illness event category, which encloses all events that cannot be filed under a specific event category. Until 2008, the relative frequency of event categories was rather stable and even after transition to acellular pertussis vaccines this was the case, although there was a decrease in absolute numbers. No events disappeared altogether, however (Figure 15). Then, in 2008, suddenly reports after booster DTP-IPV increased a lot, mainly because of more severe local reactions. This continued in 2009 and to some extent also in 2010. See under section 4.7.1 for more specifics.
relative share of the others. General illness (minor and major) remains the largest category, with a relative frequency of around 35%. Since 2008, this diminished to approximately 30% because of the increase in 4-year booster reports of local reactions.

The severity of reported adverse events is historically divided in minor and major events. See for criteria under section 3.6. In 2010, 641 major events were reported (46%; without HPV 49%), compared with 39% in 2009. During the period in which the whole-cell vaccine has been used, until 2004 inclusive, major adverse events were more prevalent with a mean of 55% (range 51.5-59.8%). In 2005-2009, after transition to acellular infant pertussis vaccine, the proportion of major events ranged from 39.0-50.5% with a mean of 45% (Figure 16A).

![Figure 16A Proportion of reported major and minor AEFI for 1994-2010](image)

For the different vaccine doses, the proportion of major events varies considerably, and reflects the type of reported adverse events (Figure 16B). Historically the highest proportion of major events is for the first infant dose. For the subsequent infant doses the proportion of major events decreases. After transition to acellular pertussis vaccine the proportion of major events decreased for all infant doses, most markedly for dose 4. The increase of major events in the 4-year booster reports reflects the prominent local reactions and a few very high fever (>40.5 °C) cases. The increase in the 9-year-olds reflects increased reporting of fainting. See for specific events under section 4.8.

![Figure 16B Proportion reported major events per dose for 2010, compared with 1996-2004 and 2005-2009](image)
4.4.2  Information Source

We try to validate and supplement reporting information by taking, as much as possible, an eyewitness account, especially for paroxysmal events. In addition, we supplement information with data from the child health clinic charts and from GP and hospital if appropriate. In 2010, we had information from more than one source in 85% of reports.

As stated before, the overall proportion of reports with just information from the reporter decreased, especially in the first 5 years since we started (1994) performing aggregated analyses of all adverse event reports, with publication of summarised annual reports. (See under section 4.2.4 and Figures 5, 6, 7 and Table 5). Figure 17 shows a break down of the decrease in the proportion of single source information. Table 8 contains the number and type of information sources per event category.

![Figure 17](image)

**Figure 17  Proportion of reports with single information source and event category for 1995-2010**

In 2010 the reporter was the sole informer in 15% (207) of reports; 74% of these single source reports concerned local reactions (76) and minor illness (76). This is similar to 2009, when 81% of the (21%) single information source reports were in the categories local reactions (47%) and minor illness (34%).

In 2010, additional information was received in 85% of reports, both spontaneously and requested, an increase in comparison with the 79% in 2009 (range 87-94% for 2004-2008). In the categories local reactions and minor illness, the increase in single information source reports is statistically significant and can be related to the (relatively) large workload in 2009 and 2010 and the relatively minor severity of the reported events.

Child Health Care Staff supplied information in 87%, compared with 84% in 2009 (range 88-95% in 2004-2008). Parents were contacted in 92% (range 87-97% for 2004-2009). Reports in which the parents were the sole informers (104) are included. Hospital specialists supplied information in 18% of the reports (range 13-18% for 2004-2009). See for further details Table 8.

In the year under report, in all cases information was requested from the National Vaccination Register (Praeventis - this is not regarded as a separate information source in the strict definition used in this section). In a few instances, batch numbers and type of vaccine were supplied by municipal health service, travel clinic or pharmacy, if available. Lareb reported 8 children to us; in one (consumer) report we could not get additional data or follow-up information from the reporter or professionals; this report is regarded as one with a single information source. The proportion multiple information sources for major events was 90% in 2010, against the 81% for reported minor events, see also Table 5.
Table 8  
Information sources and type of event in reported AEFI in 2010

<table>
<thead>
<tr>
<th>Info source</th>
<th>Local reaction</th>
<th>Minor general illness</th>
<th>Major general illness</th>
<th>Persistent screaming</th>
<th>Skin symptoms</th>
<th>Discoloured legs</th>
<th>Faints</th>
<th>Fits</th>
<th>Anaphylactic shock</th>
<th>Encephalopathy/-itis</th>
<th>Death</th>
<th>Total</th>
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<td>5</td>
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<td>29</td>
<td>29</td>
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</table>

* staff of child health clinics, municipal child health and district medical advisors of vaccination programme

For parental reports, the proportion major events is lower in comparison with the overall proportion for reports in 2010, consistently so since 1994. The year 2004 is an outlier, with a higher proportion of major adverse events reported in parental reports, but fewer have high diagnostic certainty and a large proportion depended only on the information of parents without validation or additional information. For 1994-99 combined, the proportion of single information source reports among parental reports was more or less similar to the overall proportion. Since 2000, the proportion of single info parental reports was increasingly higher than for all reports combined. For 2010, these proportions were 57% and 15% for parental and overall single info source reports respectively.

4.4.3   
Medical Intervention

The level of medical intervention may also illustrate the impact of adverse events. Figure 17 shows the relative frequencies of the different levels of medical intervention over the years. The proportion of reports with unknown intervention has diminished from over 20% to 1.5% in 2010.

In 9.4% (130) of the reports, no medical care was sought or was not reported/recorded by us (range 14-18% for 2004-2009). Parents administered paracetamol suppositories, diazepam by rectiole or other home medication 155 times (11.2%; range 9-27% for 2004-2009). Table 9 lists interventions, according to highest level.

In 78%, parents contacted the clinic or GP, called the ambulance or went to hospital, similar to 2009. The range for 2004-2008 was 57-70%. In 7.6% of the cases, children were hospitalized, similar to 2009 (8%) (range 8-11% for 2004-2009). Under ‘other’, the odd pharmacist is listed, but mainly alternative medical care (at the time of report) like homeopaths, without current regular medical care.
Figure 18A  Relative frequencies of medical intervention level in reports for 1995-2010

Table 9  Intervention and event in reported AEFI in 2010 (irrespective of causality)

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<tbody>
<tr>
<td>local reaction</td>
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<td>16</td>
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<td>27</td>
<td>93</td>
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</tr>
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<td>1</td>
<td>-</td>
<td>-</td>
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<td>discoloured legs</td>
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<td>15</td>
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<td>28</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>faints</td>
<td>-</td>
<td>17</td>
<td>5</td>
<td>67</td>
<td>5</td>
<td>28</td>
<td>5</td>
<td>5</td>
<td>14</td>
<td>18</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>164</td>
<td></td>
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<tr>
<td>fits</td>
<td>-</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>15</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>36</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>anaphylactic shock</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td></td>
</tr>
<tr>
<td>encephalopathy/-itis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>death</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>total 2010</td>
<td>20</td>
<td>110</td>
<td>155</td>
<td>330</td>
<td>111</td>
<td>386</td>
<td>15</td>
<td>80</td>
<td>52</td>
<td>105</td>
<td>3</td>
<td>13</td>
<td>-</td>
<td>-</td>
<td>1380</td>
<td></td>
</tr>
</tbody>
</table>

a  paracetamol suppositories, stesolid rectioles and other prescribed or over the counter drugs are included
b  telephone call or special visit to the clinic
c  consultation of general practitioner by telephone
d  examination by general practitioner
e  ambulance call and home visit without subsequent transport to hospital
f  mainly homoeopaths

Since 2005 the proportion of medical care for AE by the clinic has increased, since 2008 quite markedly, mainly because of the higher number of reports of pronounced local reactions after the 4 yrs booster dose (Figures 18A and 18B). In matter of fact, the proportion of the different interventions is similar over the years, if we discount the diminishing proportion of cases with unknown intervention level. However, the care by the clinic went up in the last few years and there was a reported peak in 2004 in paracetamol administration, when apprehension caused an influx of common or acknowledged adverse events.
4.5 Causal Relation

Events with the (likelihood of) causality assessed as certain, probable or possible are considered adverse reactions (AR). See section 3.7 for explanation on this subject. In 2010, 78% of reports were considered adverse reactions, with exclusion of 2 non-classifiable events. Range for 2004-2009 is 72-83% (Figure 19).

There are great differences in causality between the different event categories (Table 10) ranging between 53% for major illness and (near) 100% for local reactions. Over the years causality within each event category is very consistent. See also under section 4.8.

In figure 20, the proportion of reported events with assessed causality is shown over the years. For minor AE the proportion with causality (causal reactions) is more or less the same over the years, around 70%. For major events, there is a small trend towards lower proportion adverse reactions, especially since 2005, but still around 80%. See for description and more detail the specific sections under 4.8 and discussion in chapter 5.
Table 10  Causality and events for AEFI reports in 2010 with proportion AR

<table>
<thead>
<tr>
<th>event</th>
<th>causality⇒</th>
<th>certain- probable-possible</th>
<th>improbable</th>
<th>non classifiable</th>
<th>total</th>
<th>% AR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>local reaction</td>
<td>320</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>321</td>
<td>100</td>
</tr>
<tr>
<td>general illness minor</td>
<td>296</td>
<td>156</td>
<td>1</td>
<td>452</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>major</td>
<td>53</td>
<td>47</td>
<td>-</td>
<td>101</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>persistent screaming</td>
<td>51</td>
<td>2</td>
<td>-</td>
<td>53</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>skin symptoms</td>
<td>58</td>
<td>41</td>
<td>1</td>
<td>100</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>discoloured legs</td>
<td>96</td>
<td>2</td>
<td>-</td>
<td>98</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>faints</td>
<td>154</td>
<td>10</td>
<td>-</td>
<td>164</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>fits</td>
<td>54</td>
<td>31</td>
<td>-</td>
<td>85</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>anaphylactic shock</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>encephalopathy/-itis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>death</td>
<td>-</td>
<td>5</td>
<td>-</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>total 2009</td>
<td>1082</td>
<td>296</td>
<td>2</td>
<td>1380</td>
<td>78</td>
<td></td>
</tr>
</tbody>
</table>

* = percentage of reports considered adverse reactions (causality certain, probable, possible) excluding non-classifiable events

For local reactions the proportion causally related to the vaccinations is, as expected, very high and nears the 100%, with a few exceptions. For minor illness, the proportion of adverse reactions gradually decreased over the years, from around 80% to about 65%, with a peak again as outlier in 2004, from around 80% to about 65%. The proportion adverse reactions in the major illness category over the years fluctuates more, but is a little lower since the transition to acellular pertussis vaccines in 2005, decreasing from an average of 74% for 1994-2004 to 66% over 2005-2009 and 65% in 2010 (Table 11). Persistent screaming, as acknowledged adverse reaction, scores 99% positive causality until 2004 inclusive. Since then, the proportion of adverse reactions decreased somewhat, due to smaller absolute numbers and relatively more reported coincidental events; it is still around 95% however. For general skin manifestations, the proportion is about 55% from 1994-2004, with large annual fluctuations, and increases somewhat to around 60% in the years there after.

Figure 20  Proportion of assessed causality (AR) in reported AEFI for 1994-2010

Discoloured legs have a high proportion of positive causality, fluctuating between 94 and 98%. For the faints, the decrease in absolute numbers of reported collapse reactions since 2005, resulted in a decrease in causality proportion of adverse reactions and a relative higher proportion of coincidental spells. The increase in 2010 of the proportion of adverse
reactions is accounted for by reports of fainting in adolescent girls after the HPV vaccination. See also under section 4.8.7.

In the category of fits the proportion causally related events decreased from 77% average after the transition to acellular pertussis vaccines, possibly because less high fever and therefore fewer related reported febrile seizures and atypical attacks, leaving a somewhat larger proportion of coincidental fits. See section 4.8.8.

Table 11  Proportion of assessed causality and type of reported event 1994-2010

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>local reaction</td>
<td>91-100</td>
<td>98%</td>
<td>98-100</td>
<td>99%</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>major local reaction</td>
<td>100</td>
<td>100%</td>
<td>100</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>minor general illness</td>
<td>67-83</td>
<td>74%</td>
<td>60-69</td>
<td>66%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>major general illness</td>
<td>52-70</td>
<td>60%</td>
<td>45-55</td>
<td>51%</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>persistent screaming</td>
<td>97-100</td>
<td>99%</td>
<td>91-98</td>
<td>93%</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>skin symptoms</td>
<td>38-78</td>
<td>55%</td>
<td>57-66</td>
<td>62%</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>discoloured legs</td>
<td>94-98</td>
<td>97%</td>
<td>94-97</td>
<td>95%</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>faints</td>
<td>94-99</td>
<td>97%</td>
<td>84-88</td>
<td>87%</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>fits</td>
<td>68-89</td>
<td>77%</td>
<td>60-74</td>
<td>66%</td>
<td>64%</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>78-86</td>
<td>82%</td>
<td>72-81</td>
<td>76%</td>
<td>78%</td>
<td></td>
</tr>
</tbody>
</table>

The proportion of adverse reactions per vaccine dose is shown in Figure 21. In (combination of) inactivated (killed) vaccines, it is generally not possible to attribute systemic events to a specific vaccine or component. For local reactions, the information on exact site/side of administration of the different vaccines is often too inaccurate to make an assumption which vaccine is to blame. For simultaneous inactivated and live vaccines, attribution to a specific vaccine may be possible for some events, because of the lag time and (sometimes) the type of event. The data for Figure 20 are irrespective of the specific vaccines given at the time points in the schedule.

Figure 21  Proportion adverse reactions per scheduled dose for reported AEFI, comparing 1994-2004, 2005-2009 and 2010; for HPV all and 1st doses

The proportion of AR per vaccine dose is similar over the years. In Table 12, the mean causality proportions and ranges per vaccine dose for different periods are presented. There is very large variation between the report years. A tendency exists for lower proportions for infant doses after the transition to infant acellular pertussis vaccines in 2005. For the MMR first dose at 14 month of age the proportion is similar over the years.
with large fluctuation however. There is no difference in this respect for 2001 and before compared with 2003 and after when MenC was added simultaneously with the MMR.

Table 12  Proportion of adverse reactions for AEFI reports per vaccine dose 1994-2010

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant 1st dose</td>
<td>86-94</td>
<td>91%</td>
<td>71-86</td>
</tr>
<tr>
<td>Infant 2nd dose</td>
<td>78-89</td>
<td>85%</td>
<td>70-81</td>
</tr>
<tr>
<td>Infant 3rd dose</td>
<td>69-84</td>
<td>78%</td>
<td>65-74</td>
</tr>
<tr>
<td>Infant 4th dose</td>
<td>70-86</td>
<td>80%</td>
<td>63-73</td>
</tr>
<tr>
<td>MMR 14 months</td>
<td>49-71</td>
<td>63%</td>
<td>61-70</td>
</tr>
<tr>
<td>4 yr booster</td>
<td>60-83</td>
<td>73%</td>
<td>70-96</td>
</tr>
<tr>
<td>9 yr booster</td>
<td>55-96</td>
<td>74%</td>
<td>69-87</td>
</tr>
<tr>
<td>HPV 1st dose</td>
<td>-</td>
<td>-</td>
<td>58</td>
</tr>
<tr>
<td>HPV all doses</td>
<td>-</td>
<td>-</td>
<td>61</td>
</tr>
<tr>
<td>Total ex HPV</td>
<td>78-86</td>
<td>82%</td>
<td>72-81</td>
</tr>
</tbody>
</table>

Of course, this proportion of AR is dependent on the type of reported event. At 4 years of age, mainly local reactions were reported, with an acknowledged causal relation with vaccination. The proportion of AR for this booster has increased since the introduction of the pertussis component at this age. Causality increased for the 4 years dose along with the increase in reported local reactions and in the 9 years dose with some increased reporting of fainting (Figure 20).

For the HPV vaccinations causality was 67%, a little higher than in the catch up campaign of 2009 (61%), statistically not significant however.

4.6  Follow-up, Subsequent Vaccinations and Expert Panel Assessment

4.6.1  Feedback and Follow-up

In general, feedback is supplied to the reporter in the reporting phone call when precautions, information for parents and subsequent vaccinations are also discussed. In case the final information and assessment differs considerably from what was expected or discussed, we give feedback later, by email or telephone.

For some more severe events and for those that are complex or cause (public) concern, we prepare a detailed written assessment which is send to all medical professionals involved. These written assessments also serve as base for reassessment by the expert panel. See section 4.6.2.

Feedback and follow-up play an important role in the safety surveillance of the vaccination programme. It serves as a tool to adjust and complement the information of the report and possible sequelae of the event. It also sheds light on the result of the vaccination advice considering contra-indication and/or precautions. It is part of the guidance and education of the Netherlands Vaccination Programme.

This year will be the last year of safety surveillance in the present system. We therefore could not wait until spontaneous follow-up occurred or the planned follow-up to be carried out. We have performed expedited follow-up for the complex, pending or more severe adverse events however. We have succeeded, mainly through the clinics, in following up the majority of those cases covering some months to up to a year after the reported AE, including experiences after subsequent vaccinations. We have confidence in the diagnoses we made for 2010. Feedback of the assessment was done by phone only (1041; 75%), by
email (220; 16%) or with a full written assessment in 118 reports (8.6%). 53 reports were reassessed by the expert panel. See for break down per event category section 4.6.2 and Table 13.

Table 13  Type of Feedback per Event Category in 2010

<table>
<thead>
<tr>
<th>event feedback</th>
<th>total</th>
<th>phone</th>
<th>email</th>
<th>written assessment</th>
<th>expert panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>local reaction</td>
<td>321</td>
<td>283</td>
<td>34</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>general illness minor</td>
<td>454</td>
<td>344</td>
<td>87</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>general illness major</td>
<td>100</td>
<td>68</td>
<td>8</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>persistent screaming</td>
<td>53</td>
<td>42</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>skin symptoms</td>
<td>100</td>
<td>76</td>
<td>17</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>discoloured legs</td>
<td>98</td>
<td>71</td>
<td>15</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>collapse</td>
<td>95</td>
<td>71</td>
<td>9</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>fainting</td>
<td>69</td>
<td>32</td>
<td>37</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>fits</td>
<td>85</td>
<td>54</td>
<td>7</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>anaphylactic shock</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>encephalopathy/-itis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>death</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total 2010</td>
<td>1380</td>
<td>1041</td>
<td>220</td>
<td>118</td>
<td>53 (3.8%)</td>
</tr>
</tbody>
</table>

4.6.2  Reassessment by Expert Panel

RIVM much values a broad scientific discussion on reported particular of severe adverse events. Until 2004, GR re-evaluated a selection of severe or complex adverse events. From 2004 onwards, RIVM has set up an expert panel. This group includes specialists in paediatrics, neurology, immunology, pharmacovigilance, vaccinology and epidemiology. Written assessments serve as information for this expert panel. When appropriate additional and/or follow-up information on the cases is requested. Reported cases are reassessed on diagnosis and causality. In 2010, 53 cases were put before the expert panel. In all discussed cases, the expert panel was in full agreement with the assessment by RIVM.

4.7  Specific Vaccines

4.7.1  DTP-IPV Booster at 4 Years

Halfway 2008 there was a sudden increase in the number of reports concerning the booster dose of DTP-IPV at 4 years of age, with a reporting rate of 139/100,000 vaccinees (for the full year). This was mainly in the local reactions category. The mean reporting rate was 4/100,000 vaccinees until booster pertussis vaccination was introduced in 2002, with subsequently some increase in the reporting rate of local reactions until 2007 (mean 14/100,000 vaccinees). In 2009, the peak reporting rate was 291 per 100,000 vaccinees for the 4 yr booster dose. In 2010 the reporting rate was much lower, 125/100,000 vaccinees (Figure 22). The severity of reported local reactions was similar for 2008 and 2010 and a little lower for 2009, with around 80% of the reported local reactions qualifying as severe or extreme.

Quite some early reports of prominent local reactions in 2008 concerned children who received acellular pertussis vaccines by parental choice while the Netherlands Vaccination Programme still used whole-cell pertussis vaccines for the infant doses. In 2004, there was a lot of adverse publicity, about the effectiveness and reactogenicity of this whole-cell
pertussis vaccine. Only few parents refused further vaccinations and some bought acellular pertussis vaccines on the private market. In 2005, acellular pertussis combination vaccines were introduced for all children. We checked the infant schedule for all reported children for lot number and type of vaccine and held that against the type of booster vaccine they received.

Figure 22 Reported AEFI after booster DT(P)-IPV at 4 years of age, per 100,000 vaccinees for report years 1996-2010 (birth cohorts 1992-2006); arrow depicts start of 4y-booster acellular pertussis

The reports in 2010, for cohort 2006, had an overrepresentation of children vaccinated as infants with Infanrix-hexa, compared with the proportion of reported children vaccinated with single HepB in 2008 and 2009. This will be further studied, because an association with specific vaccines or components may shed light on the why and how of this higher (reporting) incidence of pronounced local reactions after the 4 yrs booster dose. Since the introduction of acellular pertussis vaccines for infants in 2005, 2 brand switches have occurred of pentavalent infant vaccines, with halfway 2006 the use of Infanrix-hexa for HepB risk groups replacing separate HepB vaccines.

The increase in 2008 and the decrease in 2010 coincide with several switches in infant and in booster acellular pertussis vaccines. Table 14 shows the time lines of the different vaccines. We will compare the reports with specific denominators of the vaccination register. The decrease in reports coincides also with publication and information in the RVP-news.

Table 14 Schedule and vaccines for infants and 4-year-olds over the years

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>whole-cell vaccine DT-wP-IPV-Hib (+hepB)</td>
<td>acellular vaccine RIVM-DKTP-Hib Infanrix-IPV-Hib Triaxis-polio Infanrix-IPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 doses vaccine</td>
<td>RIVM-DKTP-Hib</td>
<td>DTap-IPV-Hib(+hepB)</td>
<td>Pediace (or Infanrix Hexa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 years</td>
<td>No pertussis DT-IPV</td>
<td>+acellular vaccine DT-IPV +aP</td>
<td>acellular combined vaccine DTap-IPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>booster vaccine</td>
<td>RIVM-DTP Single aP added RIVM/GSK</td>
<td></td>
<td>Triaxis-polio Infanrix-IPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aP=acellular pertussis vaccine
wP=whole-cell pertussis vaccine
The relative severity of the reported local reactions appears to be not much different for 2009 and 2010.

Fever has been a rare reported AE after the booster dose at 4 years of age. Since mid-2008, however, fever reports increased to 5 times the number for 2007 and before. In 2010, parallel to the number of local reactions, the number of fever reports decreased again. Fever was sometimes associated with a pronounced local reaction, but some children with reported fever did not experience any local reaction.

4.7.2 HPV vaccine

In 2010, HPV vaccine was included in the RVP for girls born in 1997 with the possibility for girls, who had missed the vaccination catch up campaign in 2009, to opt in. Of the 129 reported AEFI with HPV, 39 were from these older girls; all relate to vaccinations in 2010 however. The catch up campaign is covered in detail in a special report, with results of spontaneous reports, immediate adverse event monitoring and reactogenicity questionnaires. 11,72

![Figure 23A Reporting rate per 100,000 vaccinees for different event categories, HPV 2009 campaign compared with 2010 RVP (with some catch-up campaign girls)](image)

The type of reported events was not much different in the 2 groups, 2009 and 2010 (Figure 23A). The overall reporting rate was twice as high for the 2009 campaign however, compared with 2010, 334 and 153 reports per 100,000 vaccinees respectively. However,
in 2010, relatively fewer minor events, fewer local reactions and fewer skin symptoms were reported, in comparison with 2009. The proportion of major events was 23%, compared with 13% for 2009. The proportion reports with assessed causality was 67% in 2010 and 61% in 2009 (Figure 23B). This shows a tendency towards the more severe events still being reported in 2010 and a decrease in reports of the less severe events. For the level of intervention, the proportion of girls who consulted the GP was similar for the 2 years; in both groups, 38% consulted the GP or were seen in hospital.

In 2010, about half the reports involved the first HPV dose (67; 52%) and the remainder of the reports was split between the 2 consecutive doses (39 and 33 respectively). In the catch up campaign, 77% of the reports involved the first HPV dose and 16 and 6% concerned dose 2 and 3 respectively. See for more information under the specific events in section 4.8. In general, the reported events were non-serious and concerned often age specific symptoms. No signals were detected. Some new AE were reported, being age specific phenomena, like fatigue and migraine, and rare in the younger age groups that have been vaccinated under the RVP up till now. We are checking on these events in a large GP database (IPCI).

In 2009, for HPV 127 of the reports were made by parents (20%); up to 81% of notifications came in writing on report forms, mostly from the municipal health service. The proportion single information source was 37%. For 2010 79 (61%) written notifications came in and 45 had only information from the reporter (34%); in 44 (34%) parents were the reporter.

4.7.3 

**MMR vaccine**

Reports following MMR and MenC vaccine have been stable over the years. We saw an increase in the reporting rate after the addition of the simultaneous MenC vaccine at the end of 2002. A large increase occurred in 2004, when sudden protracted adverse publicity arose. This affected also other vaccines than the whole-cell pertussis infant vaccines, with more questions and requests for advice (Figure 24). After some years, the reporting rate for MMR1 stabilised again at a little higher level than before 2002 (when MenC was added to the programme).

![Figure 24A Reporting rate for MMR1 per 100,000 vaccinees and type of events with overall proportion with assessed causality for 1994-2010.](image)

The minor illness event category is the largest for MMR reports. Actually over 90% of reports concerning the MMR1 vaccination involve only 3 event categories, minor and major general illness, skin symptoms and fits (average proportion for 1994-2010 is 95% with range 93-97%). General illness (minor and major) contributes for 58%, convulsions for 26% and skin symptoms for 11% of the reports. The largest proportion in this minor and major illness category concerns rash and/or fever, 63% on average for 1994-2010 and
together with the skin events, this adds up to 70%. Altogether, the proportion of causally related events with fever and/or rash is 53%. Therefore, nearly half of these reports involve coincidental events.

For the event category of fits, nearly all febrile convulsions, the proportion with assessed causal relation is 75% (Figure 24B). Only few are atypical attacks or non-febrile convulsions. The average proportion reported events with causal relation is 66% for minor events and 65% for major events, which contain the febrile convulsions.

The major general illness category includes ITP, an acknowledged adverse event after MMR. On average, we get 3 ITP cases reported per year (90% causally related).

Other remarkable events that are sometimes considered causally related, because no other causes could be or were established and the event occurred in a compatible time window, were arthralgia or arthritis, acute cerebellar ataxia, swollen cheeks, imbalance/walking difficulties, with on average 1.5, 0.5, 2.5, and 2 reported cases per year respectively, irrespective of causality.

We never had anaphylactic reactions reported attributable to MMR since the addition of MMR in the vaccination programme. Vaccine-attributable adverse events after the 9y booster dose are extremely rare, arguing against some type of allergy or sensitisation playing a role in MMR vaccinations. See also some specific events described in section 4.8 and under the discussion chapter.

### 4.8 Categories of Adverse Events

Classification into disease groups or event categories takes place after validation, supplementation and full assessment of the reported event. The relative frequency between and within the different event categories has changed since the introduction of acellular infant DTP-IPV-Hib vaccine (Figure 15 and section 4.4). Figure 25 shows the relative frequency per dose for the different event categories for reports in 2010. Figure 26A gives an overview of reports over the different event categories for 1994-2010.

Minor illness remains the largest reported event category, taking up around 30%. The proportion of minor illness is lowest for the 4-year booster, with its large contribution of reported local reactions. For the 9-year booster vaccinations, minor illness reports and local reactions contribute an equal proportion and the largest proportion is taken up by fainting, altogether concerning small numbers however.

An increase in the number of reports in one event category has a compressing effect on
the other event categories in this type of proportionate distribution. If rates are depicted, then this is controlled for, as shown in Figure 26B. This shows the overall increase in reports in 2004, except for skin symptoms, when there was a lot of public anxiety. Also clearly apparent is the increase in local reactions reports since 2008. Other changes are described in the paragraphs with specific events below.

![Figure 25 Relative frequencies of event categories per dose for reported AEFI in 2010](image)

![Figure 26A Proportion of reports in the different event categories for 1994-2010](image)

![Figure 26B Reporting rate per event category per 100,000 vaccine doses for 1994-2010](image)
This presentation of reporting rates per year does not take into account that some event categories contain highly age specific and dose specific adverse events, with a much higher reporting rate for these specific ages and doses. See under the specific event categories below.

On average, the sex distribution favours the boys somewhat, over the years consistently, with not much difference for the different vaccine doses as is illustrated before in Figures 13 and 14. In Table 15, the proportion of males is given per event category for 2010 and the 5 previous years. For 1994-2010, the cumulative male proportion per event category is shown in Figure 27. For sex differences per vaccine dose and reported events see under the specific event categories below.

![Figure 27 Male proportion in reported AEFI for 1994-2010](image)

**Table 15  Events and sex in reports with total number and male proportion for 2004-2010**

<table>
<thead>
<tr>
<th>event</th>
<th>sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>local reaction</td>
<td></td>
</tr>
<tr>
<td>general illness minor</td>
<td></td>
</tr>
<tr>
<td>general illness major</td>
<td></td>
</tr>
<tr>
<td>persistent screaming</td>
<td></td>
</tr>
<tr>
<td>skin symptoms</td>
<td></td>
</tr>
<tr>
<td>discoloured legs</td>
<td></td>
</tr>
<tr>
<td>faints</td>
<td></td>
</tr>
<tr>
<td>fits</td>
<td></td>
</tr>
<tr>
<td>anaphylactic shock</td>
<td></td>
</tr>
<tr>
<td>encephalopathy/-itis</td>
<td></td>
</tr>
<tr>
<td>death</td>
<td></td>
</tr>
</tbody>
</table>

* ex hpv

4.8.1 **Local Reactions**

In 2010, local reactions were the main or only feature in 321 reports, mostly following the booster DTP-IPV at 4 years of age, as shown before (Section 4.7.1). Table 16 gives a breakdown of reported local reactions in 2010.
Table 16  Reported local events of reported AEFI in 2004-2010 with number of major events and number of adverse reactions

<table>
<thead>
<tr>
<th>event</th>
<th>2010 (major)</th>
<th>2009 (major)</th>
<th>2008 (major)</th>
<th>2007 (major)</th>
<th>2006 (major)</th>
<th>2005 (major)</th>
<th>2004 (major)</th>
</tr>
</thead>
<tbody>
<tr>
<td>inflammation</td>
<td>268 (130)</td>
<td>268</td>
<td>535 (150)</td>
<td>286 (125)</td>
<td>65 (25)</td>
<td>78 (20)</td>
<td>55 (7)</td>
</tr>
<tr>
<td>abscess/ cellulitis</td>
<td>3 (3)</td>
<td>3</td>
<td>7 (7)</td>
<td>6 (6)</td>
<td>5 (5)</td>
<td>6 (6)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>pustule/erysipelas</td>
<td>1 (1)</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>atypical reaction</td>
<td>33 (2)</td>
<td>32</td>
<td>15 (0)</td>
<td>10 (0)</td>
<td>11 (0)</td>
<td>14 (2)</td>
<td>18 (0)</td>
</tr>
<tr>
<td>haematoma</td>
<td>4 (0)</td>
<td>4</td>
<td>3 (0)</td>
<td>1 (0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>nodule</td>
<td>10 (0)</td>
<td>10</td>
<td>10 (0)</td>
<td>7 (0)</td>
<td>5 (0)</td>
<td>1 (0)</td>
<td>4 (0)</td>
</tr>
<tr>
<td>avoidance</td>
<td>2 (0)</td>
<td>2</td>
<td>4 (0)</td>
<td>1 (0)</td>
<td>3 (0)</td>
<td>3 (0)</td>
<td>2 (0)</td>
</tr>
<tr>
<td>total (major)</td>
<td>321 (136)</td>
<td>320</td>
<td>571 (157)</td>
<td>313 (131)</td>
<td>93 (30)</td>
<td>102 (28)</td>
<td>93 (20)</td>
</tr>
</tbody>
</table>

The majority of reported local events (185; 58%) were classified as minor reactions. 136 Reports (42%) were considered major local events because of size, severity, intensity or duration. 115 of these major local reactions followed the 4y-booster. Common inflammation was the most prevalent aspect in 269 reports (129 considered major). 33 Reports concerned atypical local reactions with local rash or discoloration, blister, possible infection, (de)pigmentation, eczema, swelling, itch or pain, atypical time interval or combination of atypical symptoms. 2 Children had marked reduction in the use of the limb with mild or no signs of inflammation. This is booked separately as ‘avoidance behaviour’.

3 Abscesses were reported in 2010. Again no faulty procedures were detected and no suspicion that the vaccine was contaminated. 2 of the abscesses were reported after MMR vaccination. These were attributed, in the end, to the primarily not reported BCG. In one of these, following MMR0 before the age of 1 year, ulceration was reported, but a supplied photograph suggested BCG efflorescence, which indeed had been administered 1 month or so before; the other child also appeared to have been vaccinated with BCG, for planned travel, at the TBC department of the municipal health service. The other abscess was after the 4th dose of DTP-IPV-Hib (and Pneu), with spontaneous drainage 2.5 months after the vaccination. No cultures were taken and no further therapy given.

In 2010, all but 1 reported local event were considered causally related with the vaccination. This unrelated adverse event involved a rare skin condition (pilomatricoma) that appeared on an upper arm, but too far distant from the injection site. Over the years causality has ranged between 98 and 100% with 1 outlier in 1994 (91%; with in total very few reports and some atypical local manifestations considered coincidental)

For the infants the male-female ratio was near 1 but for the 4 years’ booster dose the proportion of boys was 60% and for the 9 year old boys counted for 70% of local reaction reports (Figure 28). For abscesses, more girls were reported, proportion 62%.

Since 1994, reporting rates per dose fluctuate at a low level (Figure 30). For the 4 infant doses the reporting rates range between 1 and 16 per 100,000 vaccinees, reports being most frequent after the first and 4th dose (mean 7/100,000). Reported local reactions after MMR are rare, and even after simultaneous MenC vaccination was introduced in 2002, local reactions are infrequently reported (mean 2/100,000). The range for 9-year boosters is 0-9 per 100,000 vaccinees (mean 5/100,000) since 1994.
Since 1994, 116 abscesses were reported, 101 of which occurred in infants (Table 17 and Figure 29). This is a reporting rate per vaccine dose of less than 1 per 100,000 vaccinees. For BCG we have no full information about adverse events or local or systemic complications after vaccination. This vaccine is given only to special risk groups by the municipal TBC centres (mainly). This free of charge service is not a part of the Netherlands Vaccination Programme and works without systematic reporting or registration of AE. We get reports only haphazardly. The abscesses reported to us, were 9 times primarily attributed to BCG en 3 times secondarily. For 2010 the total number of infants vaccinated with BCG was around 13,000 (TUBIS, Moree).

The abscess reporting rates for the 4 infant doses is similar. Once there were recurrent abscesses after subsequent doses in the same child and once abscesses were both sided in the legs. The majority of the abscesses were reportedly at the site of DTP-IPV-Hib-(HepB), but quite often, it was not possible to decide for sure. Some abscesses occurred at the site of single Hib, HepB or pneumococcal vaccine.

Table 17 Reported abscesses and rate per 100,000 vaccinees for 1994-2010

<table>
<thead>
<tr>
<th>Vaccine dose</th>
<th>Infant 1st</th>
<th>Infant 2nd</th>
<th>Infant 3rd</th>
<th>Infant 4th</th>
<th>MMR 1</th>
<th>BCG</th>
<th>other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of reports</td>
<td>25</td>
<td>21</td>
<td>29</td>
<td>26</td>
<td>3</td>
<td>12</td>
<td>2</td>
<td>116</td>
</tr>
<tr>
<td>Rate/100,000</td>
<td>0.8</td>
<td>0.7</td>
<td>0.9</td>
<td>0.8</td>
<td>0.1</td>
<td>0.03*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* number of doses is unsure; the number of infants is substituted, and proportion for 2010 (13,000 vaccinees)

Drainage was surgical in half of the children and spontaneously in the other half (in 10 cases we failed to record the type of drainage).

In 38%, cultures were taken. In 3%, we do not know if cultures were taken and in another, (nearly) 3% we did not get the culture results. In two-thirds, cultures were...
positive; mostly β haemolytic Streptococcus A was isolated and twice each, Staphylococcus Aureus and Streptococcus Pneumoniae. Once Mycobacterium Bovis was isolated from an abscess at the DTP-IPV-Hib injection site in the leg in a child previously vaccinated with BCG. Once, the culture was indicative of contamination.

In 59%, no cultures were taken. Only few children were treated with antibiotics. All children resumed the schedule.

63% of children reported with abscess were female as opposed to the male preponderance for reported local reactions in general.

Figure 29 shows the reporting rates per year for abscesses after infant doses. There is considerable fluctuation over the years, varying from 0-15 reports. No trend could be determined. Comparison of the whole-cell vaccine period with the acellular pertussis vaccine period does not show much difference, with rates for 1994-2004 and 2005-2009 of 0.87 and 0.84/100,000 infant doses. Even after inclusion of 2010, with only one report the 0.74/100,000 is not significantly different.

Potential cluster reports (2 or more per time period or place or lot numbers) have been followed with special attention but no common factor could be found; clusters did not persist and died out spontaneously. No relation of abscesses with eczema in the child or work of caregivers in medical (hospital) care was found.

In Figure 30, the sudden peak in reported local reactions in 2008 is apparent (139/100,000 vaccinees over the full year). The mean reporting rate was 4/100,000 vaccinees until booster pertussis vaccination was introduced in 2002, with subsequently some increase in the reporting rate of local reactions until 2007 (mean 14/100,000 vaccinees). In 2009, the peak reporting rate was 291 per 100,000 vaccinees. In 2010 the reporting rate was much lower again, i.e. 125/100,000 vaccinees. The severity of the reported local reactions after the 4y-booster was more or less similar. This signal requires more in depth analysis. See for more specifics under section 4.7.1.

Figure 30 Local reactions per vaccine dose with reporting rate per 100,000 vaccinees for 1994-2010, for HPV only reports after first dose were included

4.8.2 Minor General Illness

Minor general illness category hosts events that are not classifiable in any of the specific event categories, and, depending on severity, is further subdivided in minor or major (see section 3.5).

In 454 children, the event was considered minor general illness (Table 16). Of the reported events, 51% (233) concerned the scheduled DTP-IPV-Hib vaccinations (range 2005-2009 is 59-67%). HPV vaccinations were not included in the Netherlands Vaccination
Programme in those years, however. With exclusion of HPV, the share of infant vaccinations in the minor illness group is 61%. In the last 4 years of the whole-cell DTP-IPV-Hib period, the proportion minor illness infant reports ranged between 75 and 81%.

The summarised reporting rate for minor illness for all doses together was 46/100,000 vaccinees for 1994-2003, with again the outlier for 2004 (96/100,000 vaccinees). For 2005-2009 the overall reporting rate was 58/100,000 vaccinees compared with 52/100,000 for 2010 (excluding HPV), just not significantly different from the mean for the 5 years before.

In Figure 31, the reporting rate per dose is shown per 100,000 vaccinees. For HPV only reports after the first dose (with denominators from Praeventis) are taken into account, both for 2009 and for 2010 (rates 153 and 50/100,000 vaccinees respectively). For 2009 there was an increase in the reporting rate of minor illness following the 4 years’ booster dose (44/100,000), and in 2010 the rate was lower again but well above 2008 (26 and 18 per 100,000 vaccinees respectively).

Reporting rates for the other vaccination time points, show minor variation compared with previous years. HPV as newcomer stands out. The reporting rate for HPV is very high compared with the other vaccines (doses). Perhaps this is just because the majority of HPV reports concern events of the minor illness category (75/129; 58%) where as for other ages/vaccine doses quite some reports concern other specific event categories (Figure 23).

One must bear in mind that for HPV it concerns a 3-dose schedule, but this has been accommodated for by computing the reporting rate for only the first dose which is shown in Figure 31. As with the other vaccines, the first dose always accounts for the most reports of AEFI in general. For the category of minor general illness, this applies as well. Within the minor illness category, the distribution of the doses may differ for some events because of age specific aspects. For instance, excessive crying occurs mainly in the very young infants and fever occurs most in the 1-year-olds. Spontaneous reporting however is also influenced by subjective circumstances like anxiety, perception or unexpectedness of the event.

Only very few times a definite diagnosis was possible; mostly working diagnoses were used. As always, fever is the most prominent symptom. In 2010, 177 of the 214 reports (83%) were considered (possibly) causally related. Twice hypothermia without noted fever was reported. The majority of the reports on fever concerned the infant doses DTP-IPV-Hib with Pneu and/or HepB (126). In 26 reports, the fever occurred after MMR0 of MMR1 with or without simultaneous MenC. 23 fever reports concerned the booster DTP-IPV dose at 4 years of age and 34 concerned HPV. Only 4 times fever was the prominent feature in the reported AEFI at 9 years of age.
Table 18  Main (working) diagnosis in minor illness category for reported AEFI in 2004-2010 (with number of adverse reactions)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>fever</td>
<td>214</td>
<td>177</td>
<td>258</td>
<td>159</td>
<td>128</td>
<td>135</td>
<td>120</td>
<td>212</td>
</tr>
<tr>
<td>crying</td>
<td>36</td>
<td>30</td>
<td>33</td>
<td>64</td>
<td>56</td>
<td>61</td>
<td>57</td>
<td>83</td>
</tr>
<tr>
<td>pallor and/or cyanosis</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>19</td>
<td>11</td>
<td>16</td>
<td>20</td>
<td>83</td>
</tr>
<tr>
<td>myoclonics and chills</td>
<td>17</td>
<td>14</td>
<td>15</td>
<td>5</td>
<td>14</td>
<td>9</td>
<td>7</td>
<td>46</td>
</tr>
<tr>
<td>prolonged/deep sleep/sleeping</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>14</td>
<td>10</td>
<td>14</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>rash(illness)</td>
<td>31</td>
<td>2</td>
<td>26</td>
<td>37</td>
<td>33</td>
<td>52</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>vaccinitis</td>
<td>20</td>
<td>20</td>
<td>37</td>
<td>33</td>
<td>23</td>
<td>24</td>
<td>39</td>
<td>31</td>
</tr>
<tr>
<td>respiratory tract disorders</td>
<td>21</td>
<td>3</td>
<td>25</td>
<td>18</td>
<td>36</td>
<td>21</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>gastro-intestinal tract disorders</td>
<td>36</td>
<td>9</td>
<td>36</td>
<td>30</td>
<td>31</td>
<td>39</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>arthralgia/arthritis/coxitis/limping/imbalance/pain in limbs</td>
<td>16</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>behavioural problems/illness</td>
<td>9</td>
<td>3</td>
<td>10</td>
<td>8</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>headache, dizziness, fatigue, lethargy</td>
<td>16</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other&amp;</td>
<td>15</td>
<td>0</td>
<td>32</td>
<td>22</td>
<td>38</td>
<td>22</td>
<td>43</td>
<td>57</td>
</tr>
<tr>
<td>total</td>
<td>454</td>
<td>296</td>
<td>498</td>
<td>414</td>
<td>390</td>
<td>403</td>
<td>389</td>
<td>704</td>
</tr>
</tbody>
</table>

Rate/100,000 vaccinees (%AR) 64 (65%) 68 57 54 56 53 96

* number of adverse reactions
& anaphylaxis 1, menstrual problems 4, mastitis 1, visual or eye ailment 5

Crying was the main feature in 36 reports, as to be expected, predominantly following the first 2 vaccinations. Since the introduction of acellular pertussis vaccine for infants, pallor and/or cyanosis (11) and chills/myoclonics (27) are less frequently reported. For the other working diagnoses, numbers were more or less stable over the last years (Table 18).

This year some age specific symptoms were reported after the HPV vaccine, like fatigue, dizziness, and headache. In addition, disturbances of the menstrual cycle were reported 5 times and once mastitis of puberty. For further specifics on HPV see section 4.6.2.

Figure 32  Proportion of adverse reactions and coincidental events in minor general illness reports for 1994-2010

In 2010, in this minor general illness category, causal relation was considered unlikely in 35% of the reports (158). For 2005-2009 this range was 31-40% (mean 34%) as for the period of the whole-cell use, 1994-2004, the range for coincidental events was 17-33%
The proportion of adverse reactions decreased a little since the introduction of acellular DTP-IPV-Hib in 2005 (Tables 11 and 12, Figure 32).

For 2010, the proportion of adverse reactions in the reports varies between 81% for the first DTP-IPV-Hib and Pneu vaccination at 2 months of age and 53% for the MMR1 and MenC at 14 months of age (Figure 33). Over the years, there is some fluctuation in these percentages, but within a narrow range from 1994 until 2010.

### 4.8.3 Major General Illness

In 2010, major general illness was recorded 100 times, less than in 2009 and a little more than in 2008. The reporting rate per dose fluctuates over the years with large confidence intervals, due to relative small numbers. If the current reporting rate per dose is compared with the mean over 2005-2009 the booster in the 4-year-olds shows a significant increase. Compared with 2009 only, the increase is marginally significant.

In 2005-2006, there were relative large numbers of reports after MMR1 and MenC at 14 months of age (specific data not shown). This may be partly because for MMR the general public safety concerns continued, and the reporting threshold was a little lower resulting in more reports. These reports concerned causally related events, like very high fever (≥40.5 °C) with or without rash and some unrelated AE. In 2007, and later, both returned to previous levels. For the infant vaccines, public anxiety came to a sudden halt because of the change to acellular pertussis vaccines, with not only less reactogenicity but
also less concern. See also under section 4.7.3 for MMR vaccine and under the discussion chapter. The reporting rate per dose is depicted in Figure 34.

Very high fever (≥40.5°C) was the working diagnosis in 49 cases, against 36-123 in 2004-2009. 2 children were extremely hypothermic with a temperature (rectally) below 35°C, without noted fever before. Very high fever was most frequently reported after the DTP-IPV-Hib4 and MMR1 doses, 11 and 15 times respectively. The first 3 doses and the 4y-booster were followed by very high fever 5, 6, 5 and 7 times respectively. In 51% of reports, the very high fever was considered causally related with the vaccination (Table 18). Vaccinitis with very high fever following MMR1 was reported 6 times.

Table 19  (Working) diagnosis for reported AEFI in the category of major illness in 2004-2010 (with number of adverse reactions)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>very high fever (≥ 40.5 °C)/extreme hypothermia</td>
<td>51 38</td>
<td>53 36</td>
<td>41</td>
<td>53</td>
<td>37</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>chills/myoclonics, accompanied with very high fever</td>
<td>0 - 1</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>gastro-intestinal tract disorder</td>
<td>1 0</td>
<td>4 3</td>
<td>1 4</td>
<td>2</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>respiratory tract disorder, apnoea, respiratory insufficiency</td>
<td>6 2 13</td>
<td>8 6</td>
<td>11 7</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>meningitis</td>
<td>1 0</td>
<td>3 3</td>
<td>7 4</td>
<td>5 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vaccinitis/rash illness, accompanied with very high fever</td>
<td>9 6 6</td>
<td>15 2</td>
<td>17 13</td>
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<td>Infectious disease ns</td>
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<td>2 2</td>
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<td>5 2</td>
<td>1 4</td>
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<td>2 1</td>
<td>1</td>
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<tr>
<td>ITP</td>
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<td>2 4</td>
<td>1 7</td>
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<td>- 1</td>
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<td>1 1 2</td>
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<td>- 1 -</td>
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<td>- -</td>
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<td>- -</td>
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<td>1 5</td>
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<td>retardation/autism/pervasive-behavioral disorder</td>
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<td>2 7</td>
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<td>3 1</td>
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<tr>
<td>ALTE</td>
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<td>shaken baby syndrome</td>
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<tr>
<td>other</td>
<td>6 1 4 5 2</td>
<td>6 3</td>
<td>1 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>100</td>
<td>53 121</td>
<td>87</td>
<td>73 111</td>
<td>97</td>
<td>194</td>
<td></td>
</tr>
</tbody>
</table>

* number of adverse reactions

ITP was reported 7 times, in 4 times within the applicable risk window, twice for MMR and once each for the 4th DTP-IPV-Hib+Pnue and the 9y-booster of DT-IPV and MMR2 and thus considered possibly causally related. Apnoea and low saturation after the first infant dose was considered causally related twice. In addition, one case of arthritis (after MMR1), exacerbation of complicated migraine (following HPV) were filed as adverse reaction. In one case, possible osteomyelitis after an unfortunate introduction of a pathogen could not be ruled out, but was considered unlikely. No faulty procedures were found; the child recovered completely. In the subcategory ‘other’ were included 2 cases of transient erythroblastemia of childhood (TEC), a congenital malformation of lymph vessels (Milroy)
(and the before mentioned migraine with possible causal relation). In addition, 2 cases of narcolepsy were reported in 3-4y old children. Once symptoms were apparent around the time of Pandemrix1 or just before, with a postponed DTP-IPV booster and once with the first symptoms 2 weeks after the booster DTP-IPV and more than 4 months after Pandemrix. In both cases, causal relation was considered unlikely.

In all other reported major illness cases, causal relation was considered unlikely or absent (in case of inverted chronology). See Table 19.

See for overall causality for the category major general illness Figure 35. In 2010, the 53% does not differ statistically significantly from previous years. The proportion of causally related reported major illness fluctuates around 60% (range 52-70%) for the years until 2004. After transition to acellular pertussis vaccines, this proportion dropped to around 50% (range 45-55%). For 2010 the percentage of adverse reactions in the category major illness was lowest for the 11 months dose (39%) and highest for the 3 months dose (70%) of DTP-IPV-Hib(+HepB) and Pneu. However, absolute numbers are very small in this category, varying between 4 and 28 reports per dose for 2010. There is considerable fluctuation between the doses over the years, both in absolute number of reported major illness and for proportion of causally related events.

In Figure 36 the proportion of reported adverse reactions with causality per dose in 2010, is compared with the mean for 2005-2009 and for 1994-2004. For nearly all separate doses, the means for the 2 aggregated periods lie within the confidence limits for 2010. This is except for infant dose 4 (1994-2004) of the whole-cell period with much more very high fever reports; none of the reported major illness cases after HPV in 2009 were assessed adverse reactions, whereas 2 of the 5 reports were considered causally related with the HPV vaccination in 2010.

![Proportion of adverse reaction in reported major general illness for 1994-2010](image-url)
4.8.4 Persistent Screaming

In 2010, 53 cases meeting the case definition for persistent screaming were reported, mostly following vaccination of youngest infants (Figure 37). Exceptionally rare, 2 cases were reported after the 14 month dose of MMR1 and MenC (Figure 20). Since 1994, no reports of persistent screaming in older children have been received. Some older children may have cried for hours on end because of a different illness, like otitis media or trapped herniation, but these events will have been booked under the other diagnoses and they would have had no relation with the vaccination.

Additional symptoms were pain and swelling at the injection site, restlessness, pallor, myoclonic jerks and fever. 18 Parents gave suppositories, 13 contacted the GP and 4 children were seen in hospital of whom 2 were admitted (Table 9).

Over the years there is some predominance of boys in reported persistent screaming, the mean proportion being 58% (see Figure 27).

The overall causality for this category is very high and constant over the last years, approaching 100% in the first years (1994-1998 and 1999-2003 both 99%) and in 2004 the proportion adverse reactions was 97%. In 2005-2009, the proportion was 93%, with more coincidental events reported. In 2010 96% of reported persistent screaming was considered causally related with the vaccination (Table 10 and Figure 20). The children who cried for 3 hours and more with discoloured legs have not been booked under persistent screaming since the fierce/vehement crying is considered part of the discoloured leg syndrome.
4.8.5 General Skin Symptoms

In 2010, skin symptoms were the main or only features in 100 reports, inclusive of 7 reports after HPV, altogether 3 classified as major. For 2010, exanthema, (increased) eczema and urticaria were the most frequent reported events (83%). 9 times swelling/angio-oedema were reported. 5 reported children had petechial rash on upper body and/or face. Children with petechiae on the legs only are categorised under discoloured legs (Table 20). The subcategory 'other' includes naevus, haemangioma, discoloration, hair growth, alopecia, scar, pigmentation or depigmentation, blister/vesicles, swelling and several other rare phenomena, less than 1 or 2 per year, if any.

Over the years, this distribution has been consistent, with only a small increase in reported eczema. We will comment on that in the discussion. The reporting rate has been very consistent over the years, see Figure 26B, with rates per 100,000 vaccinees.

In 2004-2009, numbers ranged from 82-101. Reporting rates per dose differs somewhat over the years (Figure 38); this appears to be random fluctuation for the different doses.

Table 20 (Working) diagnosis in reported AEFI for general skin symptoms in 2004-2010, with number of adverse reactions (AR)

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<td>angio-oedema/swelling</td>
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<td>6</td>
<td>9</td>
<td>11</td>
<td>5</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>exanthema/erythaema</td>
<td>51</td>
<td>27</td>
<td>46</td>
<td>48</td>
<td>55</td>
<td>52</td>
<td>46</td>
<td>60</td>
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<tr>
<td>urticaria</td>
<td>13</td>
<td>6</td>
<td>10</td>
<td>16</td>
<td>9</td>
<td>18</td>
<td>7</td>
<td>8</td>
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<tr>
<td>eczema (increase)</td>
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<td>16</td>
<td>23</td>
<td>7</td>
<td>13</td>
<td>16</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>petechiae/purpura</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>2</td>
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<td>7</td>
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<td>58</td>
<td>95</td>
<td>88</td>
<td>101</td>
<td>97</td>
<td>82</td>
<td>106</td>
</tr>
</tbody>
</table>

* number of adverse reactions

For the 4y-booster, the reporting rate increased steadily from 1994 to 2010; it concerns very small numbers however (Figure 39). Taking into account only recent vaccinations with a small reporting lag time, than the increase is somewhat less (Figure 39). HPV in the catch up campaign stands out too. The rate for HPV in 2010 is more in line with reports after other vaccines and doses. The reporting rate for skin symptoms for all vaccine doses together ranges from 8-14 per 100,000 vaccinees per year since 1994.
If we regard the different types of events, this shows great heterogeneity, like hair loss, eczema, skin infection, swelling, (de)pigmentation, and all kinds of rashes. Considering the most frequent skin symptoms, urticaria or urticarial rash, shows non-consistent lag time between vaccination and event, not suggesting a point source distribution.

Figure 40A and 40B show the reporting rate for the most frequent reported skin phenomena over the years. The ranges for 1994-2004 and for 2005-2009 are similar and do contain the rates for 2010 for all events except for eczema; eczema was less frequently reported in the period 1994-2004. The fluctuation over the years is depicted in Figure 40B. For rash, urticarial and other, the rate had a step up in 2002. This was attributed to more reports for the MMR1 dose with the newly introduced MenC vaccination, without any causal relation with the MenC vaccine however. Also a little more reports for the other doses came in. For eczema, there has been no substantial increase in rates since the accelerated schedule was introduced in 1999.
Of all reported skin symptoms, 58% (58) were considered adverse reactions. For 2010, causality for the infant doses was 57% compared with the mean over 1994-2009 of 56% (range 32-74%). For the MMR dose of 14 months, since 2002 with simultaneous MenC, the proportion causality was 60% for both 2010 and 1994-2009 (range 35-82%). For HPV the reporting rate was high in 2009 and low in 2010 (all doses) but the proportion causality was similar with 30% and 29% respectively. For the other doses fluctuation is very large because of small numbers per year, the mean causality proportion for the 4-year booster was 47% and for the 9-year ]booster 51% for 1994-2010. The overall causality proportion for reported skin symptoms was 54% for 1994-2004 (range 40-79%) and 62% for 2005-2009 (range 57-65%).

For the 4 most reported skin symptoms, the proportion causally related events fluctuate around the 50% with very large year-to-year differences. This depends largely on what happened to be reported (by chance). For 2010, the number of adverse reactions is given in Table 20. Over the previous years, the aggregated causality proportions are given in Figure 41, with perhaps only for eczema an up going proportion, with small absolute numbers however. Overall, the proportionate mean causality is 55% for 1994-2009, with for the 4 most common symptoms a range of 54-63%. For the rest group ‘other’ the mean causality is lower, 47%.
Discoloured Legs

Starting in 1995, discoloured legs are listed as a separate event category, subdivided in blue, red or purple legs with even or patchy discoloration and with or without petechial rash. Petechiae on legs without noted discoloration are also grouped under this category. The same applies for swollen limbs without noted discoloration.

In 2010 we received 98 reports of discoloured legs, mostly following the first 2 doses of DTP-IPV-Hib(-HepB) and Pneu. Once, discoloured legs were reported after MMR +/- MenC. This is extremely rare, with only 14 reports since 1994. 3 Reports of discoloured arms followed HPV vaccination, compared with 4 in the catch up campaign of 2009. Like in other years, some infants had a recurrence of discoloured legs after a subsequent vaccine dose. Some children had a simultaneous collapse reaction. In most however, it concerned a single non-compound episode.

In 2010, 16 reports were categorised as blue legs (11 times double sided), 41 as red legs (25 double sided) and 27 (22 double sided) as purple legs. In 2 cases, the legs were only swollen without noted discoloration (once double sided). In 12 cases, (9 double sided) leg petechiae only, without noted prior discoloration, were reported (Table 21). Petechial rash after discoloration was reported in 8 children, 5 times double-sided.

Since 1994, the reporting rate for discoloured legs has gone up until 2003 with for 2004 a steep increase. For 2004 the reporting rate was 149/100,000 infants. The ranges for 1994-1998 and 1999-2003 were 32-66 and 63-90 per 100,000 vaccinated infants. After the transition to acellular vaccines in 2005, the number of reported discoloured legs decreased and the reporting rate for the first 2 doses was more equal than before (Figure 42). The range for 2005-2009 was 24-66 per 100,000 vaccinees for the 4 infant doses combined and for 2010, the reporting rate was 53 per 100,000 infants.

Table 21  Discoloured legs in reported AEFI in 2010 with number of adverse reactions, compared with 2004-2009

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<td>blue legs</td>
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<td>10</td>
<td>6</td>
<td>6</td>
<td>3</td>
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<td>red legs</td>
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<td>35</td>
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<td>purple legs</td>
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<td>12</td>
<td>15</td>
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<td>8</td>
</tr>
<tr>
<td>petechiae only</td>
<td>12</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>4</td>
<td>11</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>swollen limb</td>
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<td>-</td>
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<td></td>
</tr>
<tr>
<td>total</td>
<td>98</td>
<td>96</td>
<td>76</td>
<td>70</td>
<td>79</td>
<td>124</td>
<td>57</td>
<td>279</td>
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</table>

* number of adverse reactions
Since 2005, there have been many changes in the schedule and in the type of included vaccines. The influence on the (rate of) occurrence of discoloured legs and on the distribution over the different doses needs more in depth analysis, requiring detailed denominators from the vaccination register.

Causal relation with the vaccines was inferred in all but 2 cases (98%). The range for the previous 5 years for the proportion of positive causality was 94-97% and 94-99% for 1995-2004.

Numbers of double-sided discoloured legs fluctuate over the years. Until March 2003 whole-cell DTP-IPV and Hib were administered simultaneously, but in different legs. In 2005, one brand of DTP-IPV-Hib was used, with or without HepB (in a 2-dose schedule). After a year, this was gradually replaced by another brand (with or without HepB). From halfway 2006, infants born from April 1st onwards received Pneu at the same time as acellular DTP-IPV-Hib in different legs. Infants eligible for HepB received since then a hexavalent DTP-IPV-Hib-HepB together with Pneu. Before that time, in the period from March 2003- June 2006, most infants received one vaccination instead of two. This period coincides with the ‘dip’ in the proportion double-sided discoloured legs in Figure 43. One-sided discoloured legs are not always on the same side as the vaccination in the single vaccination reports. They quite often occur contra-laterally, in the non-injected limb.

In this event category, collapse (hypotonic-hyporesponsive episode, HHE), syncope (fainting) and breath holding spells (BHS) are listed (Table 22).
In 2010, collapse was reported in 91 cases. This is similar to 2007-2009, an increase compared with 2005-2006, but a sharp decrease in numbers compared with 2004 and before, the period of use of whole-cell DTP-IPV-Hib. In 62% of cases collapse occurred after the first DTP-IPV-Hib and Pneu vaccination. Numbers decreased with dose number and age, similar to 2001-2004. The 4 cases of breath holding spells occurred also after the first infant dose with DTP-IPV-Hib and Pneu; the children turned blue, after stopping to breathe in expiration when crying vehemently or after other stimuli, with a very short phase of diminished responsiveness and no limpness or pallor.

Table 22  Diagnosis in reported faints for 2010 with number of adverse reactions, compared with 2004-2009

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<tr>
<td>collapse</td>
<td>91</td>
<td>90</td>
<td>89</td>
<td>95</td>
<td>96</td>
<td>76</td>
<td>75</td>
</tr>
<tr>
<td>breath holding spell</td>
<td>4</td>
<td>4</td>
<td>18</td>
<td>9</td>
<td>14</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>fainting</td>
<td>69</td>
<td>68</td>
<td>43</td>
<td>61</td>
<td>31</td>
<td>82</td>
<td>52</td>
</tr>
<tr>
<td>total</td>
<td>164</td>
<td>162</td>
<td>150</td>
<td>165</td>
<td>141</td>
<td>82</td>
<td>133</td>
</tr>
</tbody>
</table>

* number of adverse reactions

Fainting in older children was reported 69 times of which 18 times after HPV vaccination (of which 10 times the first dose). This is apart from the reports stemming from the monitoring of immediate adverse events.

Absolute numbers of collapse reports, in Figure 44, show the increase in reports after the accelerated schedule was introduced (1999), and the continued increase because of better adherence to the early start of the schedule and a larger birth cohort as well. The steep decrease after transition to acellular pertussis infant vaccines in 2005 is also striking with subsequent levelling of numbers.

The reporting rates per dose for the 4 infant doses and the MMR dose at 14 months (collapse and BHS) are depicted in Figure 45. Figure 46 shows the reporting rates for the 4-year- and 9-year boosters and HPV, concerning fainting and near fainting (syncope).

Figure 44  Absolute numbers of reported faints for AEFI per type of event in 1994-2010

Events in this category are acknowledged adverse reactions following vaccination. For 2010, the proportion of overall causality is 94% (for collapse 90% and 100% and 99% for BHS and syncope respectively). In Figure 47, causality is shown for 1994-2010. Both collapse and fainting have very high proportions causality. For BHS, with very small numbers of reports, in 2003-2006 the proportion reports with causality was somewhat lower, caused by a relative increase of coincidental events, some driven by the adverse publicity. This event is filled by incomplete collapse reactions in the correct time interval to be assessed as adverse reaction, but also the well-known BHS in small children evoked by
vomiting, reflux or crying/temper without a proper temporal link with the vaccination are sometimes reported.

![Figure 45 Reporting rate per dose for collapse and BHS per 100,000 vaccinees in 2010, compared with the means for 1994-1998, 1999-2003, 2004 and 2005-2009.](image)

The somewhat lower proportion after transition to the acellular vaccines for collapse is the result of a decrease in absolute number of reports (with causal relation) with a constant number of coincidental events. The fluctuation in the causality proportion for BHS results from the very small numbers and relatively more reports of some very atypical coincidental events.

![Figure 46 Reporting rate of faints after 4y- and 9y-boosters and the first dose of HPV in 2010, compared with the means for previous periods](image)

![Figure 47 Proportion of reports with causal relation with the vaccinations for AEFI in the faints category for 1994-2010](image)
4.8.8 Fits

Convulsion (febrile or non-febrile) and epileptic seizures are categorised in this event category. In the subcategory of ‘atypical attacks’, paroxysmal events are listed in case no definite diagnosis could be made and convulsion could not be fully excluded either. See also section 3.5 for case definitions.

In 2010, 85 reports are listed (Table 23). Most reported convulsions were febrile (39 out of 45), occurring predominantly after the 4th DTP-IPV-Hib+Pneu (7) and MMR1+MenC (28) vaccinations. Half of the atypical attacks were febrile. Like in other years, the febrile atypical attacks were in majority in the older infants or the 1-year-olds. The non-febrile atypical attacks were more evenly distributed over the infant doses and doses in older children. This is consistent over the years.

Table 23 Diagnosis in category of fits for reported AEFI in 2010 with number of adverse reactions, compared with 2004-2009

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<td>simplex</td>
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<td>atypical</td>
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<td>4</td>
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<td>4</td>
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<td>7</td>
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<tr>
<td>non febrile convulsion</td>
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<td>6</td>
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<td>4</td>
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<td>4</td>
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<tr>
<td>atypical attack</td>
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<td>13</td>
<td>32</td>
<td>24</td>
<td>18</td>
<td>19</td>
<td>43</td>
</tr>
<tr>
<td>total</td>
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<td>54</td>
<td>83</td>
<td>88</td>
<td>69</td>
<td>85</td>
<td>118</td>
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</tbody>
</table>

* number of adverse reactions

Figures 48A (proportionate) and 48B (rate) show the different vaccine doses in the reports for the 4 types of events. The reports are divided in 5 time-periods and the 6th bar in each of the 4 blocks, gives the overall for 1994-2010 (irrespective of causality). For febrile convulsions (937 in total), over 90% occurred in the ~ 1-year-olds (blue and purple bars and lines). For non-febrile convulsions this proportion is around 50%; it concerns smaller numbers however (101). For febrile atypical attacks, with 362 reports, 60% of reports is for the 4th infant and MMR1 dose. Non-febrile atypical attacks (316) involve the younger infants in 67% (yellow and orange bars and lines).
The distribution of reports in this event category over the different doses is illustrated in Figure 49, with rates per 100,000 vaccinees for all types of reported fits together. The summarised period 1999-2004 comprises 2004 with a very high rate for reported fits, apparent for all infant doses, but most markedly for the 4th infant dose and the MMR dose in the one-year-old children (Figure 50). See also Figure 51, which plots the 3 working diagnoses of this event category for 1994-2010 (rate per 100,000 vaccinated children).

After the accelerated schedule was adopted (1999), the proportion febrile fits decreased a little for the first 3 infant doses. This had no discernible effect on reports of non-febrile fits after the first 3 infant doses. This is so with and without the outlier in 2004. After the transition to acellular vaccine, the reporting rate for febrile fits went down markedly for all infant doses with also some decrease for non-febrile fits. As to be expected, no effect on the reporting rate for fits after the MMR dose in the 1-year-olds.
The proportion reported fits with assessed causality, had a tendency to decrease, from 77% for 1994-1998, to 74% for 1999-2004 and 65% for 2005-2009; for 2010, the proportion of reports with assessed causality was 64%. This trend is more or less similar for convulsions and for atypical attacks. In none of the cases of epilepsy, the vaccination was considered the trigger for a seizure this year. In very few cases in former years, the (fever of the) vaccination may have caused a convulsion, but in none of these cases the vaccination was regarded as cause of the epilepsy or to have changed the course of the disease. See Figure 52 for causality proportions per diagnosis for 1994-2010 and Table 21 for detailed data for 2010.

The proportion of convulsions with assessed causality for MMR is constant over the years around 75% (with a rather large fluctuation between 60-90%). For the 4th infant dose, there is a tendency downward with lower causality proportion, more markedly after the transition to acellular pertussis infant vaccines. The incidence of fever and (subsequent) febrile convulsions is lower after these acellular vaccines.
4.8.9 **Encephalopathy or Encephalitis**

In 2010, there were no reports on encephalopathy or encephalitis after any vaccination. Over the years, this is a very infrequent reported event. In total, 17 reports have been received since 1994. These events followed infant DTP-IPV with or without other simultaneous vaccines in 6 cases. The event followed MMR1 in 8 children, with in 4 also other vaccines simultaneously (Hib, DTP-IPV+Hib, and twice MenC). Twice, encephalopathy followed DTP or DTP-IPV booster at 4 years and once, MenC in the catch-up campaign in an adolescent. In all but 4 cases, the event was non-related, sometimes even with inverted chronology. In these 4 events all after MMR1, no definite aetiological diagnosis was possible at the time; because of the time interval involvement of MMR could not be ruled out. In 2 or possibly 3 of these children, the fever after (or caused by) MMR may have triggered derangement of an underlying metabolic disorder, in 2 cases viral infections were equally likely. In another child, viral infection was much more likely to be the cause, but this could not be established definitely. All these 4 cases have occurred 10 or more years ago and follow-up on further diagnostics have not been received. In some of the once unresolved cases, later follow-up elucidated the cause. For DTP-IPV, we have done a late follow-up and most of the once recorded so-called pertussis vaccine encephalopathies had a different satisfactory explanation and in most even secondary involvement of the given vaccine was very unlikely. In 2011, one of the reports of the last few years appeared to have suggestive aetiological diagnosis in a specific viral infection. At the time this report, had been considered unrelated however, because of the incompatible time interval for both MenC and MMR vaccine.

4.8.10 **Anaphylactic Shock**

There were no reports of anaphylactic shock in 2010. In matter of fact, we have never recorded an anaphylactic shock after a vaccine of the RVP. Twice, since 1994, in a report received, the reported event was due to food allergens, possibly peanuts and shellfish; one of these was 15y ago and the other in 2009, after HPV. One of the events occurred several hours after the vaccination, the other on the next day. Both children have resumed their vaccination schedule uneventfully.

4.8.11 **Death**

In 2010, 5 children were reported, who died following vaccination (Table 19). The reports concerned 3 boys and 2 girls. Autopsy was performed 3 times. Without full post-mortem
investigation, a definite diagnosis is often impossible. In all 5 cases, the vaccination was judged not to have played a role in the outcome, as cause, trigger or distracter.

Table 24  Death and vaccines in reported AEFI in 2010

<table>
<thead>
<tr>
<th>child</th>
<th>sex</th>
<th>age*</th>
<th>vaccines</th>
<th>time interval illness</th>
<th>symptoms/diagnosis</th>
<th>causality</th>
<th>autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>m</td>
<td>11 m</td>
<td>dtb-ipv-hib + pneu 4</td>
<td>1m 1.1m</td>
<td>Fever on the day of vaccination. No symptoms for the next month. Then he developed fever and diarrhoea with a febrile convulsion (40.3°C). The following days, febrile convulsions continued ending in coma. He died within a few days due to total loss of higher brain functions and entrapment of the brainstem.</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>B</td>
<td>f</td>
<td>15 m</td>
<td>mmr1 + menC</td>
<td>11d 12d</td>
<td>After vaccinations no symptoms, 11 days later some diarrhoea but normal temperature in the day care centre. That same evening slightly elevated temperature (37.7 °C) and later that night found dead in her bed; autopsy showed signs of septic infection and marked abdominal lymphadenopathy. No pathogen found.</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>C</td>
<td>m</td>
<td>8 w</td>
<td>dtb-ipv-hib-hepb + pneu 1</td>
<td>5 d 8 d</td>
<td>Convulsions, vomiting and diarrhoea, dehydration and extensive cerebral oedema with loss of cortical functions.</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>D</td>
<td>f</td>
<td>10 w</td>
<td>dtb-ipv-hib + pneu 1</td>
<td>1 d 2.5 d</td>
<td>After vaccination no fever or other symptoms; perhaps some discomfort. 1.5 days later acute liver failure with subsequent multi-organ failure before potential liver transplantation. Suspected metabolic disorder, not detected. Possibly before vaccination repeatedly unexplained episodes and the few days before more listless and different smell.</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>E</td>
<td>m</td>
<td>14 m</td>
<td>mmr1 + menC</td>
<td>3d 12 d</td>
<td>Antibiotics for otitis media before and 8 days after vaccination because discharging ear and lower airway infection. Otherwise no particularities. On day 12 found in bed, not breathing, with unsuccessful CPR. He had extensive Staph AU infection resistant to the prescribed antibiotic in larynx and lungs.</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>

* age at vaccination

Every year, a few children are reported, most often infants. From 1994 until 2010, this concerned 62 infants, of which 1 received single MenC vaccine. In all reported children until now, a relation with the vaccination has been unlikely or absent. Full autopsy was performed in 50% of these children. Not always, a definite diagnosis was possible by lack of information, mostly because post mortem examination did not include full autopsy, microbiological lab tests or toxicological screening. This was the case in about 25% of reports. In 10% of cases, some adverse influence of the vaccination could not be ruled out definitely, i.e. in some children with (unstable) severe underlying illness like congenital malformations or metabolic diseases. In these cases, fever possibly caused by the vaccination may have contributed to decompensation. In addition, it has been concluded in a few instances that a severe unrelated illness has been diagnosed with delay for the reason that the vaccination was assumed to have caused the symptoms.

27 cases were reported after MMR, once administered in infancy, with or without MenC vaccination. In over 60% of cases, a full autopsy was performed. In none of the cases, the vaccination was considered the cause of death, nor to have it precipitated; in 3 cases, a
lack of information was felt. In 1 case of meningococcal B sepsis, a delay in diagnosis and late start of therapy may have influenced the outcome; here, at first, the symptoms had been mistakenly ascribed to the newly added MenC vaccination.
5 Discussion

The success of the vaccination programme, with the target diseases under control, adds to the importance of adverse events. This increases the demands on safety surveillance likewise. Mere reporting and registration of adverse events is not enough to sustain the confidence in the programme. Intensified awareness of the public and the professionals of the safety of vaccines may jeopardise the willingness to participate. In its turn, this may influence the number and type of AEFI reported to the safety surveillance system.

The demands on information and education on vaccine safety has expanded also. Easy access to up to date safety data is necessary. Parents and professionals have different wishes for safety information, which should be tailored to need.

A successful performance of the programme requires good provisions, such as safe and effective products, dedicated providers and access to the population, with good participation of parents and children, and sustained public and professional confidence. This includes also good surveillance, both of effects and adverse effects. Monitoring effectiveness and safety surveillance are not an addition to the programme but an inextricable part of it. To keep up participation, the programme needs to have good press and accessible information for all involved.

Side effects and contraindications are closely linked. Contraindications are, after all, measures to prevent side effects. Contraindications and indications are the two scales of a balance and it is this balance that drives the programme. Confidence in the programme relies even more on perceptions about safety and necessity than on objective data only. Therefore, the guidance and support of the programme is a complex activity that needs sounding antenna/feelers in the population and the professional field. Execution of the vaccination programme is an intertwined activity with adequate monitoring and adjustment. Based on sound science, we have abandoned near all contraindications against vaccinations under the vaccination programme, in the past 15 years.

In this sense, the telephone service has been a valuable tool in the guidance of the programme, with its good accessibility and highly professionalized consultation service, a low threshold tool for reporting and a good feeler for sentiments in the target population and the professional field. The interrelationship of safety surveillance and consultation service has been fruitful, with high reporting rates; it has been an adequate and quick way to address concerns and in timely reactions to false contra-indications or misconceptions.

Apart from good accessibility and sensitivity, well performing safety surveillance needs good quality of data to detect signals and trends

The requirements of the system differ from those for therapeutic drugs. Special demands must be met, i.e. specific disease entities that are not covered in MEDDRA and like coding terms, for instance persistent screaming, collapse or HHE, without confusion with hemiconvulsion-hemiplegia-epilepsy. In addition, dose numbers should be addressed, since AE may differ for different doses. The exact age is important and only generic names for vaccines are inadequate, since these biologic products may differ according to content in effect and adverse effect. Therefore, good track of lot numbers is necessary too. Injection site and device with needle length and gauge should be included also. Safety surveillance should not only be of good quality, but also transparent and verifiable.

Below, we will first discuss some results for 2010 and the strength and weaknesses of the enhanced passive surveillance system. We also will discuss the analysis and the performance of the system since 1994, which has gotten its shape over the years like a licked cub. Several acknowledged adverse reactions as well as alleged side effects or coincidental events will be highlighted, with the yield from the safety surveillance system over the years.
5.1 Safety Surveillance of the Netherlands Vaccination Programme

The backbone of the safety surveillance of the Netherlands Vaccination Programme (RVP) is the current enhanced passive surveillance system. Since 1994, RIVM has published annual reports with all reported adverse events in it, irrespective of causality. Before, the Health Council published only a selection of reported adverse events.

5.1.1 Reports in 2010

The number of reported adverse events was within expectations in 2010. The decrease of 16% compared with 2009 was the result of diminishing public anxiety and professional debate set off by the 2 large vaccination campaigns against HPV and pandemic influenza. The increased relative severity in the reports as well as the higher causality proportion point to the settling of adverse publicity. The number of consultations went down, but still some 7,000 phone calls were received in 2010. The majority of AE reports (85%) came by phone and were subjected to initial real time validation and clarification. This included explanation of further proceedings, like getting eyewitness reports from the parents and medical information from GP or hospital and additional data from child health charts. Advice on subsequent vaccinations follows preliminary assessment of diagnosis and causality during the reporting phone call. Only 16% of reports had single source information, more often in written reports than in phone reports; this was not so much because of completeness of information or the quality of data but often because of mistakes in name or birth dates or because of failure to get requested additional information. A check on the level of diagnostic certainty of the final diagnosis showed that this was lower for the written reports compared with the initial phone reports, probably because these already were supplemented and validated in the reporting phone call. The dialogue of the report by phone has advantages over the (at best) sequential monoscripts of written reports by post, fax, email, or the web.

The number of reported local reactions following the 4-year booster dose went down by half in 2010, but remains still much higher than before 2008. In the 2010 reports there is overrepresentation of children that received Infanrix-hexa in the infant schedule, compared with 2008 and 2009, when nearly all reported 4y-old children received Infanrix in the infant schedule (either Infanrix-IPV-Hib or Infanrix-hexa). Most children that received the 4y-booster in 2010 had Pediacel in the infant schedule. This signal has to be further studied, with detailed monthly denominators from the vaccination register. If indeed, the risk of local reaction is related to the type of acellular vaccine in the infant schedule this may shed light on the pathophysiology of these local reactions.

The number of HPV reports for this first year of HPV included in the vaccination programme was much less than during the campaign in 2009. The reporting rate for 2010 went down to a more realistic level with overall, a little higher level of severity and causality proportion also pointing to 'settling of dust'. The overall causality rate is lower than for other vaccines in the programme and again this year no severe adverse reactions were detected nor were new and unexpected AE. The coverage went up to about 55%.

In the following sections, some results of 2010 will be used as illustration and as a lead for further discussion of the yield of the system since 1994.

The numbers of reported events for 2010 were within expectations. The higher number of reports in 2009 is considered to be caused by the anxiety raised by the 2 vaccination campaigns held in that year, i.e. HPV and pandemic flu. This is reflected in a somewhat lower level of severity or causality and in some increase in multiple reports in 2009.
5.1.2 Enhanced Passive Surveillance System of the RVP

The enhanced passive surveillance system exists since 1962, when RIVM recognised the need at the time of the introduction of combined DTP-IPV. Then, smallpox vaccination was also monitored. From the start, a telephone consultation service has been in place, and an eyewitness account was included in the process of assessment for selected events as well. For special events, house calls or visits on site were made by a specialised paediatrician appointed by RIVM as safety officer for the vaccination programme. At the time, only few people had telephone service at home and even if they had, people felt not confident to talk on the phone, especially about personal matter. Special events of interest like collapse reactions, encephalopathies, severe local reactions after tetanus vaccination were followed-up and have had consequences for vaccination practices over the years. The system has evolved over time but some characteristics have been preserved. This includes the accessible professional consultation service, the nominal reporting and the complementation and validation of information and the follow-up of specific events as well.

Existing contraindications have been put to the test and adjusted if appropriate. Abandoned contraindications included minimum age, age to the calendar for preterm infants, family history of epilepsy or convulsions, very high fever or persistent creaming after previous vaccinations, as well as convulsions or neurological disorders, collapse reactions et cetera. These skipped contraindications have also been followed to underpin the safety of this.

An inherent weakness of passive surveillance is underreporting, all the worse if this is selective. Underreporting in the Dutch enhanced passive surveillance system has been shown to be within satisfactory limits by 2 large questionnaire studies, for collapse reactions, convulsions and discoloured legs. For some events, there is considerable underreporting especially if the lag time is long or if the event is considered evidently unrelated.

Another weakness of passive surveillance systems is the possible heterogeneity of diagnoses, both internal and external. We have addressed this as much as possible by validation and supplementation of reports and by making diagnoses according to strict criteria and case definitions. Through follow-up, we also have a late check on long-term sequels.

The availability of the vaccination register with detailed denominators is of great advantage for assessment of signals and trend analysis.

These points of consideration will be discussed in the following subsections regarding the procedures for assessment and some specific adverse events.

5.1.3 Numbers and Reporters

As stated before, reports are name based. This allows follow-up with validation and supplementation of data on vaccines, lot numbers, dates and medical information. Few anonymous reports have been received in 2010, i.e. 5 report forms without (decipherable) names following HPV and 2 cluster reports of fainters, 1 in the 9-year-olds and 1 in the HPV recipients. All other reports were nominal and open for follow-up. In our experience, it is necessary to ask for the exact date of birth (and not only age) and surname, for only then it appears possible for reporters to track down their own patients for supplementary information if requested later on. Parents fully agree to supply name and address and gladly give supplementary information themselves when asked.

Over the years since 1994, the reporting rate has gone up (with consistent and strict criteria for numbers in the annual reports), gradually and steadily with inherent fluctuations. In our opinion this reflects decreased underreporting, both in absolute numbers, in rates per vaccine dose and in specific events. Over the years, rates appear to
move around the different regions of the Netherlands, like a mop over a wet floor, straightening out annual differences somewhat. This holds for reports after the different doses and for different reported events. There is also some so-called north-south or east-west gradient in reporting, which is indeed understandable since risk perception and not only ‘absolute’ values plays an important role.

Reporting by professionals other than those from child health care staff, remains at low levels. Perhaps this level is too low, exemplified for 2010 with only 3.4% of reports by paediatricians (range 2.7-8.4% since 1994). The proportion of hospital intervention (emergency, outpatient or admission) was much higher, nearly 20% in 2010 (range 18-28%). Luckily, child health care staff serves as a kind of sag wagon, swabbing up reportable events diligently. Therefore, reports come in anyway. The same applies for GPs, who account for only 2% of the reports (range 1.1-3.5%), while in 36.5% of reports (range 33-39%) the GP is contacted in 2010.

As much as possible we have ‘counted’ adverse events per vaccinee, to avoid having more than one event per vaccination date. Only if separate events fulfilled the criteria for major and were not part of the same entity they are included in the counts separately. That applied also for events after previous or later doses, which have only been included if they were specifically reported and not only result of requested follow-up, unless it involved a defined major event. Thus, numbers are slightly inflated, since 2002 in a more or less stable proportion. In 2010, this meant an additional 7.9% of reports (including 3% for compound reports). This rule has been strictly applied to enable meaningful comparisons and trend analysis. If we would have included fever >38.5 °C, several hours vehement crying and pronounced local reactions, separately as more or less unrelated symptoms in specific other event reports, we would have had over 1000 additional reports per year. This could be further increased by counting also particular other phenomena as separate events, like all kinds of twitching, eye turns, funny turns and vomits or rashes et cetera, bulging fontanel or reddish voiding. Different computation methods create a higher or lower number of ‘reports’. The more detailed the report, the higher the multiplying factor.

5.1.4 Route of Reports and Quality of Information

Any chosen route of reporting is OK with us, as long as the reports reach us. However, some routes lead to better and more timely information than others do. In addition, some appear to be more time consuming than others.

- Reports by telephone

In 2010, as before, quite some reports come in as requests for consultation, often accompanied by remarks like “I do not call to report”, or “I do not feel the need to report”, or “do I also have to report this” after having received advice. This is true for both child health care professionals and for GPs or clinicians. Remarkably, these ‘by-product’ reports do not constitute only minor events but also severe events that the caller does not link to the vaccination but wants advice about for future vaccinations. Nearly always, these adverse events are within the reporting criteria for the vaccination programme that include severe events, unexpected events, events affecting subsequent vaccinations or causing concern and more often than not may be considered causally related in the final assessment. Some consultations concern underlying illness of medication, without AE following vaccinations of course. Adequate accessibility and quality of consultation helps along willingness to report in the future. These consultations also include ‘reports’ about (programmatic) errors and all kinds of administration mistakes as well as vaccine failures (discussed below).

Reporters often express their appreciation for this kind of dual purpose reporting. It can be used in the idle minutes between clinic appointments or with the vaccinee still present in the office. The advantage of reporting by telephone for the reporting person is obviously that it is less time consuming, especially if consultation is (also) sought. For the receiving
end, the advantage is that it is a two-way communication, with the possibility of clarifying
the information (on both ends) and discussing procedures, subsequent vaccinations and
( preliminary ) assessment of the event. It requires of course, adequate work force to
occupy the telephone service at all times. But the investment will pay itself back in time
saved and quality of data.

The vast majority of reports still come in per telephone (84% in 2010), slightly decreasing
since 1994, despite the increasing availability of other routes or methods. It is uncertain
how this has influenced the numbers, but of course, any possible reporting route should
be open.

- Reports in writing

This increased number of notifications in writing has not improved reporting quality as it
was shown by comparison. Written reports often contain just a diagnosis and lack
contributing symptoms. To offer a choice of possible symptoms to tick off does not help in
this respect, since it is unsure what is the reporters’ understanding of it; a reference to
( assumed ) pathophysiology makes this worse. This does not apply only for lay people. A
full and detailed narrative is a much better source of information, but even then, the
information does need validation and supplementation. Is reporting by telephone a
dialogue, written reporting is at best a series of mono‘logues‘. Even so-called simple
questions by mail take up more time (as we have measured) than a phone call. In the
(e-)mail reply, you often have to make assumptions for all missing information, with the
risk of the wrong argumentation. Also quite often, it is the start of several sequential email
encounters to adjust or clarify further. Certainly, ‘in writing and thus true‘ does not apply,
not for administrative matters, or for substance matters.

In written reports, the supplied information is frequently incorrect, because of illegible
writing or typing mistakes in (birth) dates or phone numbers, if supplied at all.

In nearly all instances, notifications in writing do need follow-up and very seldom, if ever,
they are ready to register and assess without need for further information. The trouble is
that the need for further information cannot be determined on the report itself, because it
is not easy to recognise false information beforehand.

The inaccuracies do not only relate to the quality of the original reports but also to the
final quality, because often it is impossible or unsuccessful to validate data on vaccines,
dates and medical information in the initial report. Also additional information and
necessary follow-up failed, because of wrong address or because replies to emails were
not returned. Consistently the written reports, while more serious contain less information.
They have a higher proportion of single information, because we were unable to get more
information. The diagnostic certainty of the diagnosis is lower for written reports than for
the reports by phone.

Therefore, it is imperative that contact information is correct on the written reports so that
information can be validated and supplemented enabling application of case definitions.
We feel that a full narrative should be supplied and not solely ticked of symptoms.

5.1.5 Validation, Complementation and Systematic Evaluation

High quality safety surveillance needs high quality data. This requires validation and
supplementation of information. Reporting diagnosis cannot be trusted as such and have
to be verified and held against specific case definitions. Only then, meaningful conclusions
on the safety can be drawn. Like in any field of data analysis, here too rubbish in means
rubbish out.

- Validation, verification, and supplementation of dates, vaccines and diagnosis

As stated before, inaccuracies in data like date of birth and sex often occur, hampering
follow-up. Worse are wrong dates of vaccinations and incorrect vaccines, since these infer
lag times and risk windows, which are extremely important in the assessment of adverse events.

Misinformation like this, is most common in written notifications but may also occur in reports by telephone because unintelligibility or writing errors or slips of the pen. Mistakes occur also in entering report info in the database. Therefore, in all reports we check information on vaccines and vaccination dates, on birth dates and sex. This is easily done when asking after lot numbers from the vaccination register.

Checking on the reported symptoms and supplementation is just as important however. The initial report information is nearly always insufficient, and in the reporting telephone call some supplementation and clarification is done as a routine. Quite often the information is second hand and not from direct eyewitness account. Vice versa, it involves only an eyewitness account but lacks the information on medical evaluation. Even seemingly clear-cut diagnoses may not be right, which cannot be checked if the report contains no narrative or detailed information on symptoms. In the late nineties, we have checked the incoming diagnoses of the reports with the final booking diagnoses and found rather big differences. The most abused diagnoses appeared to be convulsion and allergic reaction, up to the present day. This may have implications for the individual child and consequences for their vaccination schedule, but it also affects the aggregated analysis of the reports. For tabulation, signal detection and trend analysis it is of utmost importance to have homogeneous events, and not stack apples and pears (with or without some eggs or the odd biscuit).

Reporting diagnosis may differ very much from the final diagnosis, resulting from to application of case definitions on supplemented and validated information.

- Follow-up information

Follow-up on the medical history, on the course of illness or on sequelae provides further insight in the impact of the adverse events. It gives a check on the final diagnosis and on possible long-term consequences. It checks on the effect of the given advice also. Over the years this has led to further adjustments in diagnoses, in case definitions and procedures as well. This follow-up may include experiences with subsequent vaccinations too. Thus, we have checked on consequences of abandoned contraindications and the risk of MMR after ITP, for instance. This way we have reassuring data on subsequent DTP-IPV in urticarial rashes on the day of previous vaccination, on recurrence of very high fever or persistent screaming et cetera. For some events, we have performed a systematic analysis of future vaccinations or developments. This includes the rate of recurrence in discoloured legs, collapses, seizures and atypical attacks. See for discussion below under the specific events.

5.1.6 Causality Assessment

Causality assessment has been a routine part of the safety surveillance since the start in 1962. This rating has inextricable consequences for future vaccinations, both for the individual and for the population. This is not a 1+1=2 relation however. A chance occurrence after a vaccination has no implications for future vaccinations most of the time. However, an underlying disease manifest after a vaccination may influence the rest of the schedule if this disorder carries a higher risk of side effects. Lag times govern the causality assessment largely, along with the (assumed) pathophysiology of the diagnosed event. Risk windows may change over time as new scientific information becomes available. Challenge and re-challenge information is far less informative in vaccine AE evaluation than in that of drugs. This is partly because of the difference in impact in first dose or later dose antigen contact. As a rule, we use ‘unlikely’ as code for coincidental events following vaccination and ‘no relation’ only if it concerns inverse chronology (event before vaccination) or if a definite proof of a different cause has been established. Even then,
however, these cases are included in any cumulative or aggregated analysis, and all cases are reassessed regularly against new scientific evidence or new signals. Risk perception and secondary causation are included also in the assessment. Attention for additional possible causal factors individually or collectively has lead to several precautional measures. This included the 'do not cold-chain up to chilblain', at the time when cooling of the vaccination site was in fashion, with ice packs straight from the freezer put on the child’s leg. Post vaccination diarrhoea because of apple juice has disappeared again. The avoidance of any shaking of a crying child and the precaution against taking a (possibly) feverish child in the too hot parent’s bed are other examples. We include in our aggregated analysis and annual reports all reported adverse events for transparency, with inclusion of causality assessment since this is more informing than a non-assessed list of reported events as is given in the SPC’s.

Final causality assessment may differ from the initial assessment, like the reported and final diagnosis, because of additional and validated information after application of causality criteria.

5.1.7 Aggregated Analysis

The annual summarisation of reported adverse events according to age, vaccine and dose has had several implications. Case definitions and clear criteria for categorisation were necessary. It clearly is only meaningful to stack homomorphous events. Therefore, scrupulous reassessment of all report information was essential also. This is how we came across the event entity of so-called ‘discoloured legs’. In retrospect, these events had been reported before we started aggregated analysis with annual reports in 1993. They were not recognised as such, however. Reports at that time were filed individually non-coded or categorised differently by the different assessors. In the atypical attack category, several subcategories have been recognised over the years, some of which may be predictors of later disorders, like epilepsy.

Aggregation according to strict criteria is a prerequisite for signal detection and evaluation and for meaningful trend analysis.

5.1.8 Absolute Numbers, Reporting Rates, Signals and Trends

Above we have discussed numbers of reports. The Netherlands has a very stable vaccination coverage and rather stable birth cohorts too, a good reporting standard of child health care staff which administers the vast majority of the vaccines. Therefore absolute numbers of reports convey good and timely information and may be easy and early signals. As said before it is crucial to state what is regarded as a separate event. Several signals like an increase in atypical attacks/blue spells when a stronger pertussis component was used, an increase in collapse reactions following acceleration of the schedule, more reports in general, even before public anxiety was recognised in 2004 and later also in 2009, were apparent just by an increase in absolute number of (specific) reports. In addition, the decrease in 2005 after the introduction of acellular pertussis vaccine was striking, but at the same time, more than was expected and suspect of increased underreporting. The sudden increase in report numbers after the 4y-booster dose in august 2008 is another example of a signal based on absolute numbers only. Step two needs to be, to weigh this signal with the use of denominators from the vaccination register with subtotals per region and vaccine type/lot numbers. For trends, this is necessary, and to have detailed denominators at our disposal is of great advantage.

5.1.9 Results for 1994-2010

Validation and verification, eyewitness accounts and follow-up have all attributed greatly to the quality of reports. The attention to all individual reports has contributed to the confidence in the programme, by both professionals and the public. The development of
case definitions has been of great advantage, enabling meaningful analyses and systematic studies. This has increased our scientific knowledge and understanding of adverse events. We have had very high reporting rates over the years with decreasing underreporting. The large questionnaire studies from 2003-2007 have shown the good performance of more complex events like collapse and convulsions. A signal like this led to the installation of a permanent reassessment committee of the Health Council in the early eighties, on request of RIVM. The system has been very sensitive also for picking up public anxiety as was apparent in 2004 and 2009, but also in the seventies of last century and many other times. Also some early signals on regional or sub regional level have been picked up.

The three catch up campaigns have been closely followed, with, in addition to stimulated passive surveillance, monitoring of immediate adverse events and tolerability as well. Changes in schedule of vaccines have resulted in several changes in reported adverse events and were picked up by the system leading to detailed analysis and subsequent systematic studies. The telephone service has been an important tool in the safety surveillance and guidance of the vaccination programme, as should be, in consorted action. When the telephone service was overburdened, AE reports rather evaporated as was shown in the last polio epidemic (1992) with simultaneous job vacancies at the time; we have tried to avoid such unavailability as much as possible since.

5.2 Specific Events

Reported adverse events involve anything occurring after vaccinations. These events may be true adverse reactions or side effects, or chance occurrences. After does not infer caused by per se (post aut propter fallacy). However, even if the vaccine constituents have not played a role, the vaccination procedure of the fact that vaccination took place, may have influenced the outcome. Also, epidemiological data are not one to one applicable to individual cases. 2 particular events are the vaccine administration errors and the vaccine failures. After these, we will discuss some specific adverse events over time.

   o Administration errors

The telephone service has benefited the consultation for mistakes in vaccine administration and gave more insight in their consequences. The variety in errors escapes simple standardisation in remedies. In numbers, this concerns only relatively few mistakes. The impact on the provider/vaccinator is enormous however. They express invariably a huge sense of guilt and find it incomprehensible that such thing could have happened to them! The impact on the vaccinee is usually only minor. We routinely request follow-up, especially if adverse events follow the mishap. Reports included 10 times the dose from multi dose vials, mistakenly mixed vaccines or components of all kinds, half doses, double doses, extra doses after previous vaccinations, no doses or wrong devices, sites, or methods like SC in stead of IM or vice versa, et cetera. The most troublesome consequence appears to be that protection is delayed because of a missing or possibly ineffective dose. Therefore, as appropriate we have advised to administer the missing dose after all, or as soon as possible, at a different site. And, of course, to note the mistake and the current consultation and advice in the child’s chart, to check the sequence of events that led to the mistake and discuss this in the team plus to report the mistake according to the proper local procedures.

   o Vaccine failures

Vaccine failures have traditionally been reported to RIVM through the telephone service or by notification through the RIVM (related) microbiological labs. These events raise a lot of questions and concerns regarding the efficacy of the vaccine and about programmatic errors as well. Apart from that, consultation is sought for ‘repairing’ activities. Not always, the (target) illness conveys adequate immunity, e.g. pertussis or Hib. Sometimes the
vaccine failure points to possible vaccine or administration related problems, sometimes to underlying immune disorders, requiring different actions. These reports must be regarded as adverse events, but it has not been easy to have them accepted as such by the national medicine registration board (CBG or Lareb). For some vaccines, e.g. pertussis, vaccine failures are more common than for others. For Hib, only few vaccine failures occur, around 10-15 each year. For MenC none have been reported up till now, except for possibly one girl vaccinated in the catch up campaign with a rare immune disorder. Polio has never occurred in a person with at least 1 vaccination with inactivated polio vaccine. Measles immunity is very high, with an estimated protection rate of at least 97% after the 9-year booster vaccination. Now, a mumps outbreak is going on in young adults in university and college setting mainly. This is under study, with attention for batch related shortcomings, since this epidemic appears to be in a rather narrow age group. Most students report to have been vaccinated. 83

5.2.1 Local Reactions

- Common inflammation

Redness, swelling and pain are symptoms of common inflammation. This is the most frequent adverse reaction at the injection site, resulting from tissue response to the injury and to the vaccine substance. This is stimulated, to some extent, by the adjuvant that increases the local reaction of the tissue and thus the immune response. It is a sign of action rather than an adverse effect of the vaccine, within limits of course. Most vaccinees or parents do expect some level of local discomfort and do not worry too much about it. Local reactions constitute only a minor portion of categorised reports; we do not count local reactions separately, unless it is the only event or an extreme, so called major reaction. We include the severity of symptoms in the database in all instances, none the less. DTP-IPV-Hib(-HepB) and other adjuvated vaccines are more reactogenic locally as are single Hib, IPV or seasonal influenza. Vaccinees tolerate MenC rather well also, despite the fact that this vaccine is alum adjuvated.

In general, combination vaccines are more reactogenic locally because they elicit a broader local immune response. Splitting the vaccine in the different single components does not help at all, because this will lead to several local reactions and, also important for the child, 2 additional injections!

MMR causes a common inflammatory reaction very infrequently. Usually, a sharp burning sensation of short duration accompanies MMR vaccination. We do get some reports on immediate localised swelling, like a single urtica, that quickly disappears again; this is not an allergic reaction, but a local tissue response to hyper tonicity, high osmolarity or acidity of the fluid. This is of no consequence whatsoever.

Sometimes local reactions subside with some residual nodule (marble or pea) deeper in the tissue, rarely with visible retraction of the skin. 58,84,85 These nodules usually do not hinder the child and disappear in time. A check by palpation at the time of the 4y-booster in these children, showed all to have disappeared.

Haematomas at the injection site happen sometimes; these hardly ever lead to more than minimal discomfort and do not need special attention. We have not detected any carelessness in administration in those reports. Occasionally this has been the first sign of underlying bleeding disorder. Remarkably, children with later detected haemophilia do tolerate the first 3 infant vaccinations very well mostly. Children with significant bleeding or clotting disorder as a rule, get the vaccines deep-subcutaneously in the thigh, and not intramuscularly. In the MenC campaign the children vaccinated SC were not more troubled by local reactions than their peers, as became apparent in a group followed-up through their haematologist (Peeters, AMC). This is consistent with our experience.
Atypical local reactions

Every year, some reports involve atypical local reactions, like hair growth, pigmentation or depigmentation, and naevus-like blotches. The vaccination is no cause of this; sometimes this could not be determined for sure, however. Occasionally, local rashes have been reported e.g. blister-like, urticarial, vesicle or petechial rashes. These rashes usually were short lived and not allergic in origin, underpinned by uneventful revaccinations. The pathophysiology remains unclear. Occasionally, fixed drug reactions are suspected; however, these are without consequences too.

Rarely some persistent eczematous reaction occurs locally, with repeated scratching adding to it. This demands symptomatic management and has no impact on subsequent vaccinations.

Increased local reaction reports after the 4y-booster

The increase of reported severe or extreme local reactions after the 4y-booster is described in literature. The pathophysiology remains unclear. The reaction is not just a response to the chemical action of the vaccine, nor the primary immune response, because the risk increased a lot, since children had acellular pertussis vaccine as infant schedule. This year, the risk appeared to be influenced by the type of acellular vaccine in the infant schedule. This will be further studied. Such a link might shed light on the how and why of those local reactions. We have no reason to believe that the increase is due to an increase in local infections, but quite a few children received systemic antibiotics. In our view, this is unnecessary but we understand that in an individual case it may be hard to differentiate. That the reaction subsides soon after start of the antibiotics does not affirm infection. Nor does application of antihistaminic (topically) affirm allergic origin. We informed child health clinics and GPs about this specific local reaction and its interpretation in 2009. The relative severity of the reported local reactions appears to be not much different for 2009 and 2010; therefore a decrease in reporting willingness and the wearing off of the novelty factor, is not a likely explanation for the decrease in reports. See also under discussion under sections 5.1.1 and 5.3.4.

Future changes in the programme have to be followed scrutinously for this type of adverse event.

Abscess and superficial infection

Abscess at the injection site is an infrequent event. We have found no relation with abandonment of local disinfection procedures. In general, no faulty procedures have been detected in individual cases and neither an association with eczema of health care employment of parents. Hypothetically, these circumstances could increase the risk of skin contamination by pathogens. In the Netherlands, less than half the abscesses are cultured. In the majority of the cultures (67%), a pathogen has been isolated, mainly *Haemolytic Streptococcus A*. We have some doubt that sterile abscesses occur in the modern vaccine era and do not regard just negative cultures a rock solid basis for this. Abscess occurs most common in infancy, in majority ascribed to the DTP-IPV(-Hib)(-HepB) vaccine although some have been documented definitely at the site of single Hib, HepB or Pneu vaccine. Some reports were after MMR vaccine, but quite a few of these appeared to involve reaction to previous BCG. For children receiving the MMR0 or other vaccines for travel in the second half-year of life it may be better to use the right arm or inject in or over the triceps region, in order to avoid subsequent confusion.

With the common modern vaccines, sterile abscesses are rare, if they occur at all.
5.2.2 Collapse (HHE) and Fainting

- Collapse or Hypotonic-Hyporesponsive-Episode (HHE)

This event has been on the payroll since the early fifties of the last century. The first descriptions leave some doubt about the nature of these events, however. Hopper used the word collapse and this still has our preference. HHE is a tongue breaker for non-native speakers and misses reference to the main symptom of the event, i.e. pallor. The other names of the entity through the years, like shock-like-syndrome or shock-collapse, give entirely the wrong notion in suggesting some kind of shock. Since the seventies, we have used a case definition for collapse, which we have adjusted and tapered in 1993. Later the Brighton Collaboration has also defined collapse (HHE) with further adjustment to make the case definition less sensitive and more specific. 65,90,91,92,93,94

Collapse is a paroxysmal event with sudden pallor, limpness and loss of consciousness (not attributable to another illness), with all three symptoms fully or partially present. In atypical cases, the colour may be blue/cyanotic and some children have hyper-tonicity instead of hypo-tonicity. Just one or two of the triad is not enough to qualify for collapse reaction. All young children may be somewhat pallid and limply when not feeling well.

Collapse is most frequent after the first infant vaccinations, and the rate of occurrence decreases with subsequent doses. Collapse appears to be both dose-dependent and age-dependent. 95 The first dose at 2 months of age results in more collapse reactions than the first dose at 3 months. In addition, a second vaccine dose at 3 months results in far fewer collapse reactions than the first dose at 3 months.

Collapse usually does not recur after subsequent vaccinations, as has been determined for our reports in 1994-1995, when the contraindication was lifted. 96,97 The estimated rate of recurrence was 0-2%. Since the accelerated schedule in 1999, the collapse rate increased and so did the rate of recurrence (estimation ~4%). After transition to the acellular pertussis vaccine, the risk of collapse decreased to about one third. 44,45,46 The rate of recurrence was equal however, also around 4%. If collapse recurs, the symptoms are usually less intense.

Collapse has long been thought to be specifically caused by the whole-cell pertussis vaccine. We have some reports however of collapse reactions after DT-IPV vaccine or single Hib or HepB vaccine. These are rare however, but perhaps not so much, because the risk is lower, but because, by design, we always vaccinate with pertussis vaccines in young infants. Despite thorough studies no relation with certain vaccine constituents have been found nor to certain responses in the child, like glucose levels. 98,99 Long, it has been thought that endotoxin of the whole-cell pertussis vaccine was to blame, but acellular pertussis vaccines do not contain endotoxin, therefore this theory does not hold. Critics have doubted the collapse reactions after acellular pertussis vaccines to be true collapse reactions, but our robust series do not support that.

Since 1994 until 2004, we have included over 2000 collapse cases and in most, we have taken detailed eyewitness accounts by one of our specifically experienced doctors. Since 2005, we have followed another 500 cases of collapse. The presentation is similar for the two periods and the distribution over the doses as well. Perhaps the frequent changes in used vaccines (brands) in the acellular pertussis era, has influenced the risk of collapse after subsequent doses somewhat (with more frequently some 'new to the body' antigens) and subsequently some levelling of the proportion collapse after first and second doses (69%/19% versus 53%/24%).

Collapse occurs with a peak around 3-4 hours after the vaccination and lasts between a few minutes till several hours (exceptionally, when children drop off asleep and are still very pallid and limp but perhaps not unresponsive anymore). The first symptom to appear...
is the pallor, which is also the last to go. Some collapse reactions in infants occur shortly after the vaccination like the fainting in older children.

The pathophysiology of collapse remains un-elucidated so far. First thought to be a sort of neurological phenomenon, now we interpret it as some kind of vaso-motor event. This surfaced, after having heard descriptions of over 2500 cases. The frequent accompanying symptoms underscore this, i.e. transpiration, dilated pupils, swallowing, dripping saliva, yawning and the like. Common are also away turning eyes. Some children have hypertonicity with or without jerks (as sometimes also occur in fainting). Remarkably common are some provocative circumstances, like crying, apnoea, vomiting, defecation and rectal temperature taking or depositing a supp. Some events occur post-prandial or during feeding.

We have followed children, not only for the subsequent vaccinations, but also with respect to their development. We have no signals of adverse lasting effects of collapse reactions at all. A preliminary case control study in children up to the age of 2.5 year did not show any untoward results and no differences between the 2 groups. Numbers were limited however and we have started a larger case control study in pre-adolescents.

For parents of young infants, collapse can be a frightful experience with their child suddenly turning ashen, flaccid and unresponsive. How to prepare parents for this rather rare event remains under debate. In the whole-cell period, the rate was about 1 per 1000-1500 first doses and now it is about 1 per 3000-4000. Detailed description of the event in advance scares all parents and some may be opting out altogether. Better perhaps, is telling parents to expect the more common adverse events, such as local reactions, fever and listlessness with crying and pallor, loss of appetite and disturbed sleeping or increased sleepiness. Instruct them what to do about these. And to tell them that if anything happens that they do not trust or are worried about, not to hesitate to contact the GP. Worse than being uninformed about a possible adverse reaction, is to overlook something needing therapy because the parent thought it to be the expected adverse event. It remains like sailing between Scylla and Charybdis.

- Fainting

Fainting or syncope is a common sequel of injections and thus of vaccinations as well. This event sometimes occurs before the vaccination or even at home while mentioning the appointment. Some reports concern a child that had its own vaccination uneventfully but in watching another child’s vaccination fainted. One adolescent was in the shower the next day while removing the band aid and thinking how brave she had been; then she fainted and in the fall moved the thermostat with resulting severe burns on the back.

Fainting is regarded an innocent event, but injury could be a severe consequence. In addition, it could set off turmoil at the (mass) vaccination setting and induce sequential panic or set off fainting in others. Differentiation between fainting and other immediate adverse events may not always be easy, especially if rashes appear. Chances of allergic reactions to programme vaccines are extremely low, if occurring at all. Fainting does not require medication and careful composed evaluation is warranted and will calm down bystanders. In mass settings one should be prepared for this, panicky behaviour of those in charge does no good, nor do ambulance sirens and the like. Undue or unfounded diagnoses like anaphylaxis, or epileptic seizure in children fainting with jerks, are harmful. Vaccinees afraid of allergic reactions (may be rightly so because of personal history), are more prone to fainting with or without rash of flush. These and other over-anxious people are best to be vaccinated in a separate room away from the crowd. For people prone to fainting, of course, it is best to let them lie down, in order to prevent fainting and trauma. Spontaneous reports to the system on fainting are very rare, mostly involving the 9y-booster dose. In HPV vaccination, fainting is relative common as well. Often it is not the
fainting per se, but the fear for an allergic component in the train of events that governs a report. Quite some of these events are reported when a next vaccine dose is due.

We monitored the catch up campaigns carefully for immediate adverse events. In the MenC campaign, we wanted to assure preparedness for them and to contribute to preventive logistics, such as a reassuring environment, adequate staff and procedures for all imaginable events. For the MenC, HPV and H1N1, the rate for faints was similar. For MenC the peak rate was in the 9-13-year-olds with sequential sex predominance of more males in the younger age groups and more females in the older. The rate for the most prone age groups was 21/10,000 vaccinees (6-14 years). The HPV campaign concerned selected age groups of girls only (13-16 years, cohorts 1993-1996) and H1N1 involved mainly the very young children (0.5-5 years) and some older family members too. The rates for HPV were ~20/10,000 (13-16 years), and for H1N1~24/10,000 (6-17 years) for first doses, both with relatively small numbers however; the MenC estimate was within the confidence intervals of the 2 other estimates.

5.2.3 Discoloured Legs

Discoloured legs as an event, is a direct benefit from the effort towards the first annual report. The necessity to tabulate different events and the careful re-assessment of all reports left us with some rather striking and similar descriptions. These certainly did not satisfy criteria for local reactions or any other acknowledged adverse event. A search in the literature did not give any lead. We decided the term ‘discoloured legs’ fitting, after we encountered it in a Swedish questionnaire we were asked to review. None of the Swedes could explain at the time, or later on, its inclusion in the questionnaire. Sifting records, we found several reports that fulfilled discoloured legs in the 4 years before 1994. Therefore, the event was not specifically linked to the newly introduced Hib vaccination as we speculated at first.

The event includes a sudden discoloration of one or both legs, not originating from the injection site. The extension may differ, but if double sided, is often rather symmetrical. It may involve the entire leg, from groin to toes or even from belly button downward. Also just a part of the leg may show discoloration. The impression is stockings, pants or like socks and even sometimes ‘knee warmers’. The discoloration is even or patchy. Discoloured legs may be one sided or both sided, even if only one vaccine is injected; it may be one sided but definitely in the other leg. Conversely, it may be one sided with vaccinations in both legs, but the side does not foretell which vaccine is to blame. Several parents have noted the discoloration to start in the feet and expand upward. Most parents however, have not seen it develop. In the early phase vehement crying accompanies the discoloration most of the time; this lasts for 10 minutes-1 hour, or even longer. This gives the impression of extreme discomfort or pain. The rest of the skin may be pale or ashen and/or feel clammy.

Blue legs often are cold and are seldom swollen; the duration is from minutes to several hours. On the contrary, the red or purple legs last longer, sometimes for the rest of the day. These red or purple legs are frequently swollen and warm to the touch and petechiae may follow. Sometimes these petechiae show the next morning unexpectedly and when asked, some cases exhibited fierce crying for some time on the day of vaccination and perhaps the discoloration went unnoticed.

Petechiae on the legs usually do not increase further after detection, and may take several days to disappear again.

This event is most common after the 1st vaccination and the risk decreases after the 2nd, 3rd and 4th dose, though less steeply than in collapse. In the whole-cell vaccine period, 50% of the reports were after the 1st dose and ~30% after the 2nd. After transition toacellular pertussis vaccine the proportion was more equal after 1st and 2nd dose (40%
each), but similar for 3rd and 4th dose, i.e. 16% and 5%. We have not studied the event to the same extent as collapse. Nevertheless, there is clearly more risk after the first 2 doses, than after later doses. The reporting rate for discoloured legs decreased to 2/3 after transition to aP. But still about 90 cases per year are reported for the infant doses annually (1/2000 infants vaccinated).

The time interval of this phenomenon is the same as in collapse, e.g. in a rather narrow normal distribution around 3-4 hours (2-6 hours) after vaccination, with also a small hub in the immediate post vaccination period. Some reports involve discoloration of the legs longer after vaccination, but these are rare and if occurring after 24 hours the likelihood of causal relation is small. Some children report having this phenomenon also before the (sometimes first) vaccination and some children report repeating discoloration weeks or months after the index vaccination. Therefore, this event is apparently not mono-specific for (certain) vaccinations. For petechiae, we allow a somewhat longer time interval to consider it possibly caused by vaccination. Since we include reports in our analysis irrespective of lag time this does not influence numbers.

After other vaccines, at older ages, the risk is very small and the system has only few cases over the years, usually involving the arms. The so-called extended limp swelling (ELS) after booster doses, does not fit the presentation of symptoms nor the time distribution of the discoloured leg syndrome.

The rate of recurrence is low, but somewhat higher than the 4% for collapse, with sometimes skipping a dose (not the child but the event). Estimation is 5-10% recurrence at most. Discoloured legs and collapse do occur in the same vaccinee, most often simultaneously, estimated around 7-8%. Sometimes discoloration occurs in a child that had collapse after previous or later vaccinations and vice versa. This is altogether much more often than expected by chance alone, being collapse-rate X legs-rate. We expect this phenomenon to be vasomotor in pathophysiology because of this and because of the set of accompanying symptoms as well. 64

5.2.4 Convulsions and Epilepsy

It is not easy to diagnose convulsions, they have a broad range of symptoms and very rarely an EEG is available. 66,104,105,106 The diagnostic certainty is often low. The type of symptoms depends on age, on location and on spread of cerebral activity. This having said, it is easy to understand that any paroxysmal event may be a seizure. However, not every child that jerks or turns its eyes is having a fit. Quite some events reported to us as seizure are collapse reactions, sleep myoclonics, pavor nocturnus, tantrums, apnoea or breath-holding spells, fever delirium et cetera. By careful history taking and by application of different case definitions for different epileptic presentations, we have tried to disentangle the reported seizures. We code them in categories of febrile and non-febrile convulsions, in febrile and non-febrile atypical attacks and in epilepsies or in any other relevant diagnostic group.

Reported convulsions are 90% febrile and 5% non-febrile, on average; at the time of assessment, another 5% of reported convulsions were considered expressions of existing or subsequently diagnosed epilepsies. Follow-up of 1368 cases (1301 children) of (possible) seizures (convulsions, myoclonics and atypical attacks) over a period of 10 years (1997-2006) has shown that some children developed epilepsy later on, ~7%, most commonly in reported children with the more complex or atypical presentations, both in lag time and in presentation of symptoms, at the time. Some of these children had simple febrile seizures first and developed unrelated epilepsy later. 15 children were diagnosed with Dravet Syndrome with SCN1A mutation later on. These children have their epilepsy not because of the seizure after the vaccination, but the seizure may have been a (first or early) manifestation of the disorder. 107,108,109
Febrile convulsions

In young children, febrile convulsions are the most common seizure event. The age range is 0.5-5 years, with a peak between 10 months and 2 years. Febrile convulsions may occur before or after this age-range but chances are higher that these are symptomatic convulsions, and not just seizures provoked by fever (pattern).

Not surprisingly, the reported febrile convulsions follow mainly the vaccinations at the age of ~1 year. For the 4th infant dose the reporting rate had been about 1.2/10,000 infants and after the transition to acellular pertussis this rate decreased to about half, 0.6/10,000. The report year 2004, with its public anxiety, produced an outlier in the reporting rate of about 2/10,000, perhaps because of decreased underreporting but also with lower diagnostic certainty of the diagnosis however.

The reporting rate for the first 3 infant doses is low, but also decreased to half after the accelerated schedule was adopted, from 3.6 to 1.8 and further to 1.3 per 100,000 infants after acellular pertussis vaccines. The febrile convulsions in the young infants are mainly after the third dose at a higher age.

For convulsions after MMR1, the reporting rate has been rather stable, in the first years after 1994 increasing due to diminished underreporting from 1.1 per 10,000 to 1.7 per 10,000 vaccinees. After the introduction of simultaneous MenC the reporting rate went up somewhat further to 2.1/10,000 but still involving mainly the MMR risk window and very infrequently that for MenC (first 24 hours, with sometimes an extension if appropriate fever pattern/course).

Simple febrile convulsions contribute to 55% of reported convulsions with fever. In 10% of reports the febrile seizure has an atypical course, like tonic or atonic presentation or is not specified enough to categorise. Complex febrile seizures attribute 35%.

Previous febrile seizures are no contraindication anymore for any of the vaccinations. If children develop fever after vaccination, another febrile seizure may develop. The cause of the fever is not significant herein. This is not easy to prevent however, except for measures like cool clothing and not putting the child in the parents’ bed. Paracetamol prophylaxis appears not effective in preventing febrile seizures in illness. For vaccination however, with predictable fever, this is not studied yet. In whole-cell pertussis vaccines the rate of fever was around 50% after the 4th dose, in which case paracetamol prophylaxis could be an option (if early enough, long enough, high enough and often enough administered). In acellular pertussis vaccines, the risk of high fever is much lower and paracetamol prophylaxis is less rational. For MMR the risk of fever is low also, ~10% and not easy to predict when to occur. Therefore, for MMR vaccination we have never advised paracetamol prophylaxis at all.

Of reported children, around 4% had convulsions after both the 4th infant vaccination and MMR1.

In the last 6 years, in about 75% of febrile convulsions the vaccination was (possibly) the cause of the fever. The incidence of fever and (subsequent) febrile convulsions is lower after acellular pertussis vaccines. The occurrence of coincidental events remains the same obviously, and if they continue to be reported this increases the relative proportion of these coincidental events. In addition, if underreporting diminishes, there is an inherent increase in reported coincidental events.

Non-febrile convulsions

Reports of non-febrile convulsions are very infrequent. They constitute about 5% of reported seizures with an equal distribution over the 4 infant and MMR doses. The transition to acellular pertussis vaccine has not influenced this, nor has the addition of the MenC vaccine. This does suggest non-causality of non-febrile convulsions with vaccinations, in the first place. Non-specific triggers related to vaccination may cause
these non-febrile convulsions, but epidemiologically this does not show in an increased risk in the first 24 hours (unlike for the febrile convulsions). In these children, another (not yet diagnosed) underlying illness may be present. Although the vaccine did not cause this underlying illness, even if it sometimes actually triggered the convulsion, these disorders might cling to the vaccination, and smudge the safety record of it wrongly.

This is the main reason to postpone vaccinations in children suspected of some underlying, not yet diagnosed neurological illness. One must realise that this protects the vaccine against allegations but leaves the child unprotected from the disease. Therefore, this should be weighted carefully. It will be of help, to explain explicitly to parents beforehand, that vaccinations do not influence the course of an underlying disorder on the long run, but that the target disease may well have adverse consequences for the child.

Non-febrile convulsions after a previous vaccination do contraindicate subsequent vaccination, with the above remarks in mind. The causality for non-febrile convulsions is lower than for febrile convulsions; in the last 6 years, 60% is possibly triggered by the vaccination on average.

- **Atypical attacks**

  The category of atypical attacks is a kind of repository for undefined paroxysmal events for which convulsion could not be ruled out definitely. By definition, these events are non-specific heterogeneous and their number is greatly influenced by chance. Reporting rates went up since 1994 until 2003 with a peak (doubling number) of the reporting rate in 2004. The events are divided in febrile and non-febrile atypical attacks.

  Febrile atypical attacks are evenly distributed over the first 3 infant doses and twice as many after the 4th dose. Since the transition to acellular vaccines, the reporting rates decreased from nearly 4 to 1.5 per 100,000. For MMR the rates increased from an average of 2.3 to 3.8 after addition of MMR, irrespective of causality. This is not attributable to MenC vaccine constituents because only very few events are in the risk window for MenC.

  For non-febrile atypical attacks the highest reporting rates are in the youngest infants, in which twitches, jerks and funny turns are the most common regardless of vaccinations. For the 1st infant dose the rate went down from over 4 to 2.5 per 100,000 vaccinees after transition to acellular pertussis vaccines. For doses 2, 3, 4 the rate is around 1 per 100,000 on average and for MMR+MenC 1.5/100,000 vaccinees.

  Causality was 75% for reported febrile atypical attacks and 41% for non-febrile atypical attacks, in the last 6 years. Both rates were somewhat less than after whole-cell pertussis vaccines.

- **Epilepsy**

  In some reported children, underlying epilepsy may cause convulsions or other paroxysmal events. These events are categorised under convulsions or atypical attacks with the appropriate causality label. If epilepsy was diagnosed in the immediate follow-up period, before final assessment for the annual reports, these reports will be booked as epilepsy. In these children, convulsion or atypical attacks that were possibly triggered by the vaccination have been also categorised as such. Fits in children with pre-diagnosed epilepsy will only be booked as fit and not as epilepsy.

  We very seldom get children reported with already diagnosed epilepsy with a seizure after the vaccinations, despite epilepsy not being a contraindication. It is uncertain if this is because these seizures do not happen in close time relationship with the vaccination or because seizures are expected and/or within line of expectations and therefore perhaps not reported. Epilepsy is a rather common childhood disorder. 112,113,114,115,116,117,118,119

  As mentioned above, follow-up showed about 7% of children reported with possible fits to have developed epilepsy in a 10 years follow-up study. In some, there was already some
developmental delay or other signal for neurological illness. Some of the children appeared to have developed epilepsy apparently totally unrelated to the post-vaccination episode. This study aimed to detect Dravet Syndrome (DS), for which presentation of the AEFI was atypical in timing and course. This is another example that some underlying disorder is the cause of events after vaccination, triggered or fully coincidental. Awareness of this may accelerate diagnosis and perhaps beneficial early treatment. Even an unrelated underlying disorder may affect the perceived safety of the vaccinations. 120,121,122,123

Most reported cases of epilepsy concern West Syndrome (WS). This disorder is typically one of young infants, sometimes with underlying neurological disorders but sometimes without any (cryptogenic). WS is an, gradually, evolving epilepsy in which the attacks are getting more frequent and more specific in time. It is conceivable that the vaccination could be a trigger in some children, but in most reports parents or family recall earlier, at the time unrecognised, atypical movements in the child. Occasionally, after the diagnosis of WS, on hindsight, they remember some attacks after an earlier vaccination; it is usually hard to decide on exact time relationship in these cases. Epidemiologically, WS does not have a link with vaccinations. 124,125 In Denmark, the age of debut did not move with the change in vaccination schedule. 126 For some types of WS, an increase in incidence rate is observed in the first week after vaccination, with a compensatory decrease in later weeks. 127 This points to increased alertness of parents in the post-vaccination period, leading to earlier diagnosis. It could also point to the vaccination being a trigger of latent epilepsy that would have become apparent in the following weeks any way, as the compensatory reflects.

5.2.5 Persistent Screaming

A long known adverse vent following childhood pertussis vaccination is the so called persistent screaming. 62,124,128 For one reason or another, this is often booked under neurological reactions, making it more ominous. 129,130,131 Is it because of the thrill pitch of the young infant shriek, ‘encephalitic-like’, or because of the difficulty to interrupt. However, this high pitch is the normal sound of crying in the very young, regardless of the cause. It appears to be more a signal of undefined ‘not-feeling-well’ than a specific adverse event. 132,133,134 The risk of excessive crying is very high in very young infants, with the incidence depending on case definition, varying from a few to up to 17% of young infants. 135136,137 The increment attributable to the vaccinations, and if at all, only for one day, is minor. No relation has been found with local reactions or any other objective adverse event. 138,139 But surely, this inconsolable intractable and vehement crying works on the nerves of parents. Often this occurs after the first vaccination in the very young infants, with the parent left worrying if it will ever stop and about the underlying cause, coincidental or vaccine related. 140 The frequency was certainly higher after whole-cell vaccine than after acellular pertussis vaccines. 141,142,143 In follow-up most children resumed their schedule and no long term sequelae have become apparent. 144,145

5.2.6 Allergic Reactions, Anaphylaxis

Allergic reactions are the ultimate fear of everyone administering vaccines. This is theoretically possible of course, but in actual practice, more a phantom than reality. Statistics differ in different studies and settings. Perhaps, differences in applied case definitions or the lack of these are to blame. Descriptive, symptomatic and aetiological diagnoses are intertwined and clarifying follow-up is often hampered by abandonment of further vaccinations, governed by fear.

The new case definitions do not help very much in this regard. 68,146,147,148,149 This new case definition is hard to apply since the combination of symptoms from different tracts and different grades of severity is arbitrary, open for debate or for personal discretion of
the practitioner/clinician. These symptoms from different tracts should (believed to) be part of a common single aetiological pathway and not caused by unrelated factors; pruritic rash because of whatever and wheezing because of bronchitis caused by an airway infection should not be included. Should symptoms be simultaneous, and what interval between is allowed? Not only events with an immediate allergic pathogenesis (IgE mediated) are included, as before, but now also non-allergic anaphylaxis (anaphylactoid) events find a place. Aetiology is different and often policy regarding subsequent vaccinations is different as well. Problem is that the diagnosis of anaphylaxis in (not only lay) people’s minds is still that of allergy, with strong reluctance to continue the schedule, to put it mildly.

We have recoded all reports in a 10-year period by selecting all cases booked as urticaria, urticarial rash, itchy rash, and/or swelling or angio-oedema and checked if dyspnoea in any form was present, and vice versa. Common cold symptoms were excluded and rash illnesses with fever as well. Only very few cases were detected, with in the narrative often suggestion of divergent timing and duration. In diagnosis allergic reactions, the result of administration of antihistamines is of no help, even if a relief of symptoms followed. Apart from the post aut propter dilemma, antihistamine medication is expected to relieve symptoms caused by non-IgE mediated mast cell degranulation.

Our experience with vaccines in the Netherlands Vaccination Programme has been very favourable. Even in children who on hindsight fulfilled the case definition for anaphylaxis more or less, further vaccinations appear to be uneventful. This goes for DTP-IPV and combinations, for HepB and Pneu but also for MMR. Also for influenza vaccine in egg protein allergic children, the vaccination with a minimum level of surveillance (staying in the clinic for 30 minutes) seems to be quite adequate. The most common symptoms appear to be urticarial rashes with or without swelling. See also below under urticarial rashes.

5.2.7 Rashes and Eczema

Only very few studies have been performed on skin phenomena and vaccinations, apart from eczema vaccinatum after smallpox vaccination obviously. Most reports are anecdotal case descriptions or at best (follow-up of) small case series. This is perhaps a sign that in general there is no real or frequent concern.

- Urticarial rashes

Rashes are very common in children and often of viral origin. The so-called typical distribution for a defined viral illness is very often absent and in children with a specific childhood disease with this typical specific rash, a different virus may be detected. A specific rash illness is very hard to diagnose on clinical appearance only, unless perhaps in a defined epidemic. Atypical rashes are often the reason for reports after MMR vaccination, even if they occur right within the risk window (5-12 days, peak 9-10 days). Frequently, these reported rashes are urticarial with or without itch or swelling of eyes and ears (sometimes hands). Reporters fear allergic reaction, and wonder about subsequent vaccinations. These rashes are non-allergic and to be rated as atypical viral rashes with or without fever.

Most urticarial rashes are non-allergic and in children often of viral origin. In addition, toxic/chemical and physical stimuli may evoke urticaria. A cow is an animal, but not all animals are cows, the fire engine is red but not all red cars are fire engines. Therefore, urticaria diagnosing as allergic reaction is jumping to conclusions and in assessment, the time interval with the suspected trigger is of importance too. Follow-up of suspected cases may shed light on causation and consequences also.

We followed reports of urticarial rashes, itch and swelling over a 10-year period. The time interval after DTP-IPV (and combinations) is random and does not have a point source
distribution, neither are several interval clusters apparent. Subsequent vaccinations are usually uneventful or have the common mild post vaccination symptoms; if urticaria recurs at all, these are not more intense nor with severe other symptoms.

We have neither formulated a contraindication for any of the reported children. Sometimes precautional measures were taken, not so much for medical necessity but more for reassurance purposes. Careful assessment is always necessary to underpin the safety of the programme. Both parents/vaccinees and providers fear possible allergic reactions.

- **‘Vaccinitis’**

  After MMR, sometimes rashes occur in the immediate post vaccination period; these also have never met our criteria for allergic reaction to the vaccine until now. More common are rashes in the 2-12 days after the vaccination. In combination with fever in this risk window we call this ‘vaccinitis’. This vaccinitis occurs in 5-15% of children, with 20% of children having fever (peak on day 8-9) and 15% with rash (peak day 10). Like in other viral rashes this vaccinitis sometimes has atypical presentation with urticaria and/or swelling of face, ears or hands/feet. This does not point to an allergic reaction. In few children the rash gets confused with the natural infection, and these may be reported as measles. Needless to say, that serology or PCR is not helpful in determining the cause since after vaccination one would expect an immune response and the virus to be detectable. Of course some labs are able to differentiate between vaccine virus and wild type virus, but this appears a waste of effort. Chances are very remote of infection with wild type measles virus in exactly this risk window after MMR vaccination. Later rashes than starting within 12 days are coincidental, but then also chances of natural measles infection are slim since the vaccine has a >95% take.

- **Eczema**

  Eczema is a very common skin disorder in infants. Parents and providers often wonder the role of vaccinations in eczema. Before the acceleration of the schedule, more children had already eczema before their first vaccination than with the start at 2 months of age. Now we see more eczema appearing after the first vaccination than before. This is not because the vaccine causes eczema but because of the natural course of the illness. Eczema fluctuates on all kinds of stimuli like the weather and intercurrent infections or fever. Some children may experience an increase in intensity or distribution in the days after the vaccination. This is to be regarded as possible non-specific stimulus also and not as an allergic reaction to vaccine constituents. The vaccines do not contain cross-reactive substances with food allergens. Some children have an improvement of their eczema for some time after each vaccination, but this is not often a reason to report. Any influence of vaccines on eczema is limited in time and does not aggravate the course in the long run. Eczematous children may have even more benefit from vaccination than average since they often are more prone to airway infections. The small increase noted in the last few years of reported eczema seems to point towards increased attention rather than to higher incidence.

**5.2.8 Encephalopathy or Encephalitis**

The pathways of medicine are strewn with the wrecks of once known and acknowledged truths (quote from Barbara Tuckman). One of these wrecks is the pertussis vaccination encephalopathy. In analogy with the known post-vaccinal encephalitis or encephalopathy after smallpox vaccination (which should be spelled as post-vaccinal instead) and with the feared brain damage after pertussis infection, unexplained encephalopathy has been ascribed to pertussis vaccination in the past. Quite some encephalopathies have their peak age of occurrence or manifestation in the age group in which we vaccinate. By chance alone some are expected after vaccination. More in depth analysis of cases and
epidemiological studies have shown that encephalopathy is not a consequence of pertussis vaccination. \cite{67,116,117,121,122,123,125,164,165,166,167,168,169,170,171,172,173} Also further diagnostic possibilities for genetics and virus detection have diminished the unaccounted for encephalopathies. Nevertheless, still up to today some events do not get an aetiological diagnosis. It is no wonder that parents and clinicians point the finger at vaccination in some cases. There is, of course, no proof of absence or of a negative association. What is not there, you cannot catch. In some cases the (fever or vomiting after the) vaccination may have tipped the scales, e.g. in underlying severe metabolic disorder and may have caused derangement and encephalopathy. Also, some children with underlying encephalopathy or developmental disorders, cope less well with stress and illness and may present with more exaggerated symptoms related to relatively common adverse events.

MMR is a live vaccine and as in infections may theoretically cause either direct viral encephalitis or immune mediated encephalopathy. \cite{174,175} The first occurs earlier than the second does. The number of post-measles or post-MMR encephalopathies that do not get an aetiological diagnosis dwindles, but still in some children, no final aetiological diagnosis is possible. In some of these cases, MMR as causal factor cannot be ruled out definitely. The frequency of these unaccounted for events, is lower however than that of unaccounted for encephalopathies on average i.e. background rate. In the past 17 years, altogether 17 cases of encephalitis or encephalopathy were reported to the surveillance system. 9 cases occurred after inactivated vaccines of which 5 in infants and 3 in older children. Of the 8 reports following MMR, in 4 cases no satisfactory aetiological cause has been established (up till now) and because of the time interval, relation with MMR could not be ruled out definitely. This is on nearly 3.5 million first MMR vaccinations.

We have to keep up being vigilant for possible severe adverse events. The truth of today may be the wreck of tomorrow; vice versa today’s wrecks may be tomorrows truths.

5.2.9 Death, including sudden infant death syndrome

Since children die, some reports following vaccination may be expected also. The most common cause of death is infection, next to congenital disorders. These latter do not very often confuse us, unless it concerns not yet diagnosed problems, like metabolic disorders. Infections can only be diagnosed after occurrence and may happen unexpectedly. The same applies to sudden infant death syndrome (SIDS), by definition without cause. In these cases, parents and providers may suspect the vaccination. It is imperative to report death cases if they occur in a defined risk window and be evaluated for possible direct or indirect influence of vaccination. This could be very easily accomplished, since all children are covered in the vaccination registers in which all administered vaccines are entered. In the Netherlands, therefore we have an exemplary possible design to perform an appropriate study, without curtailing confidentiality. It is also possible to study the role of vaccines in aggravation of the disease as a secondary factor this way.

In the past 17 years, 60 infant cases following DTP-IPV (or combination) and 27 after MMR1, with or without MenC, have been reported. SIDS, or clinical SIDS in case of insufficient post-mortem examination, was the most common diagnosis. Invasive bacterial infections were the second most frequent finding. Derangement of (suspected) metabolic disease was the third cause of death. Several children had underlying structural malformations. 2 children died because of leukaemia, several years after the vaccinations. In about 5-10% of children, no diagnosis was possible. A little less than 50% of infant cases had a full post-mortem examination and around 60% of cases after MMR.

In 25% of infant cases a lack of necessary information was felt. Nevertheless, in only few children a secondary role of the vaccination could not be ruled out fully, because of time interval and lack of diagnosis. This involved 6 times DTP-IPV (combination) vaccine with possible derangement of a not defined metabolic disorder or very severe other underlying
illness. After MMR, in 3 children some secondary influence of MMR could not be excluded definitely. In all these cases, causal relation was considered unlikely however.

The supposition that in Japan the incidence of SIDS decreased after postponement of pertussis vaccination to 2 years of age, is based on a misquote. The time association disappeared but not SIDS. Obviously, this condition with an unknown cause has been studied also in relation with vaccinations. No study has found any suggestion of a causal relation. The steep decline in SIDS in the Netherlands, with over 200 cases per year down to 10-20 cases with similar vaccination coverage (and many more components) underpins this finding. 176,177,178,179,180,181,182

For hardly any underlying illness, the vaccinations are a risk. International studies support this. Vaccination may induce derangement indirectly in some metabolic disorders that are easily deranged by fever and/or vomiting. In addition, some structural severe cardiac malformation may be jeopardised by any stress or exertion. In some very severe immune-deficiencies, live vaccines may have adverse consequences (apart from lack of efficacy of the inactivated vaccinations); live vaccines are contraindicated but for MMR we have not heard of any mishaps in this respect. All these disorders are extremely rare and conversely, they constitute a higher risk from the target diseases as well. Vaccination is usually warranted, with a shifted risk-benefit balance, if anything. In some children with a specific severe underlying illness, as mentioned above, vaccination may take place under a precautionary regimen.

In one child reported to us, and possibly some others, late diagnosis because of mistaken attribution of the symptoms to the vaccination has delayed appropriate diagnosis and treatment. This may be the most severe adverse event after vaccination for which we all have to guard against.

5.2.10 ITP

Immune or idiopathic thrombocytopenia (ITP) in children is mostly an acute and self-limiting immune-mediated disorder, after infections or suspected (viral) illness. The peak age is approximately 2-4 years (1-5 years). The system receives several cases of ITP every year, mostly after MMR vaccination but some after other vaccines like DTP-IPV in infancy or after the 4y booster. For MMR, the distribution of the reported cases suggested a possible causal link. In addition, natural rubella and measles infections are quite often complicated by ITP, therefore in analogy this could happen also after specific live vaccines. In a surveillance study through the Netherlands Paediatric Surveillance Unit (NSCK), we have found such a link (2002-2003). This was consistent with studies in other countries, be it that the risk we found was somewhat higher (as estimated in case only design SCCS). We found that approximately 1/20,000 children vaccinated with MMR1 developed ITP. All children recovered quickly and no severe complications occurred. In most children this occurred in the 3-4th week after the vaccination.

In this study, there was a small signal of an increased risk of ITP after the infant vaccinations, but it concerned very small numbers and if any increase in risk it is an extremely rare condition. This needs further study. For the MenC campaign in 2002, no signal whatsoever was generated. We have not received reports of recurrence after subsequent vaccinations in any of the children, regardless if the ITP followed vaccination or not. Most children with ITP after the first MMR have received the second dose at 9 years, up till now uneventfully.

Even if MMR causes ITP in some children, it also prevents ITP, since the risk after natural infection of ITP is much greater than after vaccination. 183,184,185,186
5.2.11 Autoimmune Disorders

Several immune-mediated disorders or autoimmune diseases have been studied with regard to vaccinations. Sometimes, this concerned the (contra-) indications for specific vaccinations and sometimes it involved the role of vaccinations in the development or aggravation of the disorder. It is understandable that this focuses on illnesses frequent in the age group of the vaccination schedule, since then the risk of any adverse event is more prominent. In general, autoimmune disorders are not linked to any of the childhood vaccinations, even if they are administered in late childhood, adolescence or adulthood. As said before, some immune-mediated disorders could, theoretically, be caused or triggered by live vaccines. This has not been indicated by any study however. 124,175,187,188,189,190 (See also under encephalopathy above)

- **Diabetes mellitus**

  Diabetes Mellitus (DM) is a long known and frequent childhood illness, without elucidated cause however. In Finland, the introduction of Hib vaccine coincided with an increase of DM. We, in the Netherlands, had a similar increase but we were late introducing Hib vaccine; therefore, an inverse chronology occurred here. Later re-evaluation of the Finnish data cleared Hib from allegations. All other vaccines before (pertussis vaccine in Sweden) and later have passed scrutiny in this respect. Therefore, vaccines are not a cause for DM and all the more indicated in DM. 33,191,192,193,194,195

- **Multiple sclerosis**

  In the mid-nineties, a HepB campaign in adolescents (universal) and young adults (risk groups) induced an increase in multiple sclerosis (MS) reports to the vigilance system. This created public anxiety, although the reports were in line with expected numbers of incident cases or relapses, compared with the background rate. Later several expert committees (WHO and Institute of Medicine-IOM, GR) have reviewed available information and concluded that there was no indication for a causal link, theoretically, in experimental studies or in epidemiological information. Later systematic controlled studies have underscored this and found HepB vaccination to be unrelated to MS or relapses of MS. 32,196,197

- **Reactive arthritis and juvenile idiopathic arthritis**

  For some vaccines, reactive arthritis as immune-mediated disorder cannot be ruled out in all instances as a consequence. This applies for the live MMR vaccine for which some reports come in each year. In literature, some case histories have been published as well. No systematic studies have underpinned a relation between this condition and vaccines and if there is a relation in some individual cases, this adverse event is very rare and seems comparable with the background rate. We apply a risk window of 6 weeks for MMR and expect a possibly related case to occur in the 3-4th week. In all possibly related reported cases, the condition cleared fully and no persistent joint disease followed. Rubella wild type virus, perhaps mumps virus, and several other viruses and bacteria may cause reactive arthritis but they are not the cause of rheumatoid arthritis (RA) or juvenile immune arthritis (JIA). Several vaccines have been studied for the risk of incident JIA or relapse in JIA, but have not found an indication for a relation. 198,199,200

- **Guillain Barré syndrome**

  Guillain Barré Syndrome (GBS), also an immune-mediated disorder, has been linked to some special kind of swine flu vaccine in the seventies of the last century. Later re-analysis has shown there to be a very small increased risk. Later influenza vaccines have given no such indication. None of the other vaccines are linked to GBS. GBS may follow several viral infections or suspected viral illnesses but no definite or strong relation has been found. The risk of GBS following influenza infection appears to be greater than after vaccination, however small. To be prepared for introduction of new vaccines, international
studies have monitored background rates of several immune disorders, including in the Netherlands. 201,202,203,204,205

- **Plexus neuritis**

Occasionally plexus neuritis (parsonage turner syndrome or neuralgic amyotrophy) is reported, but in the last 17 years none of these cases were consistent with the case definition and/or with time interval for vaccine causation. Most reports in literature are about single cases and most are on single tetanus vaccine (or immunoglobulin). In the meantime more knowledge about this immune mediated disorder has been gained, and viral illnesses seem to be the probable cause, most notably parvovirus B19 (5th disease), apart from physical stress, with or without genetic predisposition. Epidemiologically no link has been found with any vaccination. 191,206,207

- **Acute cerebellar ataxia**

This postinfectious immune mediated disorder sometimes has a temporal relationship with vaccination. It is only very rarely reported after RVP vaccines. In a study in collaboration with NSCK we found no relation with the current RVP vaccines, but association with varicella infection was confirmed. Minor coordination problems or imbalances are sometimes reported. Some may be due to local reactions of vaccine administration in the thigh, Some have been diagnosed as coxitis fugax, for which no link with mumps vaccine virus has been found. Other non-specific gait disorders have not been linked to vaccination 208,209,210,211,212 Especially with such non-specific or rare diagnoses other aetiologies should be kept in mind in order prevent harmful delay in intervention.

- **Narcolepsy**

In 2010, 2 cases of 4 year old children with narcolepsy have been reported, both probably incited by adverse publicity in July 2010 after a signal from the Nordic countries of narcolepsy following H1N1 vaccination. Further evaluation of the Finnish and other Nordic cases showed a 6-10 times increased risk. 213,214,215 Bias and confounding could not be ruled out. This increased risk has not been confirmed in other countries. Some studies showed association with infection with the pandemic influenza A(H1N1) virus. 216 Historically encephalitis lethargica was a notorious complication of the spanish flu of 1918-1919. 217 For other vaccines an association with narcolepsy has never been found.

### 5.2.12 Retardation, Autism and Behavioural Problems

It is understandable that parents and sometimes also clinicians, look at vaccines with special concern, if an illness develops shortly after a vaccination. This is especially so if it involves a disorder with an unknown cause. We indeed all search for an answer to the why-and-the-why-me question. 218,219

- **Retardation and neurological disorders**

Developmental delays are often without an aetiological diagnosis, at first. The age at which we vaccinate, is also the age in which quite a few of these conditions become apparent. As said before, pertussis vaccine has been cleared from causing or triggering encephalopathy, but we get a few reports every year of children with developmental disorders or neurological illness. For some, eventually an unrelated cause has been found. That relieves the vaccine from allegations, but not always so for all. 116,124,196,220,221,222

- **Autism and autistic spectrum disorders**

Autism, or autistic spectrum disorders, manifests itself when demands on communication increase often in the second year of life, sometimes with signals of poor communication already in the first year. A faulty study linked autism to first measles virus/vaccine and later to MMR. 36,37 This study proved to have several flaws and later the authors have been
pilloried and were even expelled from their medical society, but the harm has been done. Several studies have since cleared MMR vaccine from any such allegation. Also pertussis vaccines, with or without thiomersal have been shown to have no relation with autism. 223,224,225,226,227

As stated before, children with this kind of developmental disorder often have coping problems with situations of fear, stress and pain, like happens in vaccinations or in other illnesses. This is a consequence of the disorder, but sometimes parents blame the later apparent disorder to this post vaccination episode.

5.2.13 Susceptibility for Infection and Immune Overload

Another returning discussion and worry is that stress of the vaccinations pose a threat to the young or immature immune system. For some vaccines, the strength of the immune response is less in young infants than in older children or young adults. For most however, the immune response is quite adequate and the vaccines address the system for what it is designed. The vaccines do not overwhelm the immune system and are not a so-called immune overload. Even with 10 vaccines given together, only a small part of the full potential is addressed, and the used naïve immune cells are quickly replaced. 228,229,230

Often heard is the supposition that vaccination may lead to increased susceptibility for (other) infections. The reasoning behind this is that the immune system is so busy with the vaccine that other pathogens might enter unnoticed. Epidemiological data point the other way, that the risk of common airway and gastrointestinal infections occur less than expected by chance. 231,232,233,234,235 This is also true for severe and invasive bacterial infections. There even seems to be a long-term non-specific beneficial effect of vaccinations, most notably suggested for measles vaccinations. 236,237,238,239

Some experimental animal studies suggest that activation of the immune system by vaccination diminishes the risk of unrelated infections. Medically speaking, there is no reason to postpone vaccination in a sick child. Illness and vaccination do not interfere. 240 It may not feel very refined to pester a sick child further, but if not too severely ill, the vaccination may be given after all. However, the interpretation of the illness might be hampered, with the risk of delay in proper treatment. In reality, this is always the issue, even in a child perfectly healthy at the time of vaccination. Therefore, put the vaccination in the differential diagnosis, nothing less but certainly nothing more. Always be aware of an unrelated illness requiring special attention.

5.2.14 Coincidental Events

Coincidental events after vaccination are the most frequent AE. Anything in life may indeed occur after vaccination, after all. Trends have to be watched for unexpected changes, when new vaccines are introduced. International data exchange is necessary also, especially for rare events to add to numbers. In case of severe or worrying adverse events, coincidental or not, it is best not to take a premature decision on subsequent vaccinations. That is best left, to a later date when the commotion of the acute phase has subsided and a full assessment can be made. 27,28,50,51,188,189,241,242

5.3 Summarisation of Adverse Events for Specific Vaccines

The safety surveillance system has supplied a lot of valuable information through the years. The reporting rate has been exceptionally high, compared to comparable systems in the world. Underreporting has been limited and changes in vaccines and schedules have produced several signals that could be followed-up systematically. The system has been very sensitive for public anxiety also. The detailed validated information has led to new
information on specific adverse events. Below we will discuss some of the effects of programmatic changes with regard to the different vaccines in the schedule. More details for the different vaccines and what adverse events to expect is given in Appendix 3A-3B.

5.3.1 Neonatal Hepatitis-B Vaccination

For this neonatal dose, introduced in 2006, the lack of reports is most notable. We have some doubt that awareness of possible adverse events is up to standard and initially adverse events were only marginally mentioned in the guidelines, if at all. It could well be that in the neonate fewer adverse events occur because of the special transitional state it is in. Symptoms may be less recognised as well. Some common adverse events like fever and local reactions are less frequent in the very young (premature) infants. Effectiveness and efficacy of neonatal vaccination appears to be quite satisfactory, both for HepB and e.g. for pertussis of tetanus as well as for BCG. For HepB the long-term immunogenicity is not much decreased by the simultaneous gift of specific HB Ig. Only few Dutch infants are vaccinated immediately after birth with HepB0 (around 500-600 per year), therefore not many reports are expected anyway. BCG is not given routinely at birth and for risk groups, usually sometime in the 2nd half year of life. In total about 13,000 infants are vaccinated annually (TUBIS, Morée, Amsterdam)

5.3.2 Infant Vaccines, DTP-IPV, Hib, HepB, Pneu

The basic vaccine and most troubled vaccine (vice versa) at this age is DTP-IPV, since the late fifties of the 20th century. Other vaccines have been added over time, but the safety profile for these added vaccines as sole/single vaccine has not been determined in large (unselected) same-age-groups (Hib, HepB, Pneu). Not always generic product comparisons are adequate, since composition differs. In addition, interaction occurs between the different components in combination vaccines. Therefore, it is too simple to blame only the pertussis component itself for increase in reactogenicity when comparing DT-IPV with DTP-IPV. Not only different D and T contents/potencies, but the whole-cell pertussis component also acts as adjuvant and increases the other components’ immunogenicity. Likewise, this interaction might also increase the reactogenicity of the entire combination. Still, only the pertussis component gets blamed for anything following. This continues to the present day also for the acellular pertussis component.

Pertussis vaccine has been held responsible for several serious conditions in the past, of which it has now been cleared scientifically. This involves e.g. (deterioration of) neurological illnesses, retardation, encephalopathy and epilepsy. Successively, several alleged effects have been crossed off the list. What remains, is the common reactogenicity, which is indeed higher for whole-cell combination vaccines than for acellular pertussis combination vaccines. The abandonment of specific and non-specific contraindications for pertussis vaccine has turned out well. Systematic follow-up has shown this to have been the right action. Not only pertussis vaccine as such, but also additives or residual substances have been under fire. Thiomersal in infant vaccines has been named as a cause for autistic spectrum disorders, concentration or attention deficit disorders, several other developmental problems and encephalopathy. Studies have shown that there is no ground for this. The Dutch vaccination programme has never used vaccines with thiomersal, however.

New vaccines, especially if for new age groups, may lead to an increase in reports of age specific adverse events. This is to be expected, because incident cases were not reported to the pharmacovigilance systems before. New interventions may also increase attention or awareness. This may be interpreted as signal for causality and create public anxiety with all consequences. This occurred in France after the adoption of universal HepB infant and adolescent vaccination with in its slipstream adult HepB vaccination. This was followed by with an increase in reports of MS. Likewise, in Germany a new surveillance system led...
to an increase in reported SIDS after vaccination. For neither of this a scientific indication has been found. HepB vaccines have been used in several hundreds of millions infants all over the world by now, in single formulation or in combination. The track record is excellent, for safety and for efficacy. The pentavalent HepB vaccines have been in use for 15 years or more and the hexavalent vaccine has been registered in 2000. Before that, clinical trials have been done in the target group (infants) and after registration, a lot of comparative studies have been performed in infants with different vaccines and schedules and also in premature infants. These hexavalent vaccines are as efficacious and safe as the other vaccines.

- **Schedule and vaccine changes**

Over the years, the infant schedule underwent several changes. The surveillance system has picked up several signals. After addition of simultaneous Hib vaccine, the reporting rate increased, with possibly an increase in discoloured legs as well. The stronger pertussis component (1998) led to some increase in atypical attacks. The accelerated schedule resulted in an increase in collapse reactions. The further increase in collapse was shown to be associated with better adherence to the early start of vaccination. This also influenced the discoloured legs rates. In 2003, finally combined administration of DTP-IPV-Hib was approved, reducing the necessary injections. This paved the way to add another risk group for HepB, i.e. infants of parents from middle and high endemic areas in the world (approximately 10-15% at that time). We have not noticed a marked change in reported events after this. In 2004, the vaccine had not changed but the perception did. Intense public, political and professional debate influenced the reporting rate, both for major events, real and perceived. Already in the first week of the year within a few days of an adverse television programme, the number of reports doubled.

A political decision led to the transition to acellular pertussis vaccines; a decrease in reports followed. After this so-called honeymoon period, some increase in reports followed in the next years. This coincided with a gradual change to a different acellular vaccine brand. In addition, Pneu vaccine was added and for HepB eligible children a hexavalent vaccine. Some effect could be seen on reporting rates, however these were not clinically significant. In 2009, 2 large campaigns (HPV and pandemic H1N1) led to a lot of questions and consultations and, inherently, reports. In 2010, the infant schedule did not change, but adverse publicity subsided.

The system has shown to be very signal sensitive. The fact that not all changes had an exact starting date or applied to full cohorts has hampered the study of signals. It was easy to retrieve the exact vaccines and lot numbers on individual level, but denominators for month of vaccination, per vaccine dose and vaccine brands could not be supplied routinely from the system.

- **Effects of changes on the vaccination coverage**

Notably, the vaccine uptake continued its high levels of over 97% for the primary series of DTP-IPV, despite all the changes in schedule and perception. If anything, newly added vaccines lag behind only a little bit (not more than 1-2%). The proportion of DT-IPV, with skipping the pertussis component, has decreased to less than 0.5%, after abolishment of the specific contraindications, and fully since 1996. The vaccination register is of great importance as well. From a paper file, initially for remuneration of providers, it now is a centralised database updated daily from municipal population registers. It enables individual registration and follow-up (reminders), as well as monitoring and subsequent (specific) action on (regional) population level.

The continuous high coverage is greatly the result of the dedicated providers in child health care, with professional skills, expertise, attitudes and competence. This should not be taken for granted and requires continuous effort from all involved. It requires sufficient, comprehensive and timely information on all levels of depth for professionals and parents.
The new media require special formats and a wide range of material and methods should be available, from colouring books to web based toolkits.

The possibility for second line consultation for professionals needs to be secured and is of great importance for parents in showing that their problem is taken seriously. That the consultants need to be well-informed, skilful and competent, goes without say. Just quoting a line from a book is not enough. Information about the why and how, rightly tapered to the specific situation at hand is of importance. In this respect, the existing consultation service has surely contributed to confidence in the vaccination programme. The centralised consultation service has offered a helicopter view not only on safety, but also on acceptance and possible breaches in confidence. It also radiates a relevantly caring government, to both professionals and the public. (Signalling being there for you)

- Effects of additional simultaneous vaccines and of combination vaccines

As stated before we have not found clinically relevant differences between combined DTP-IPV-Hib vaccination and simultaneous Hib. Of course, local reactions were more frequent with separate injections. Local reactions at the Hib site were less frequent and less severe however. Vaccines given time spaced gave an added frequency of adverse event compared with simultaneous administration. The risk of true adverse reactions is higher (e.g. twice fever and listlessness, in stead of once) but also the chance of (possible) coincidental events doubles if vaccines are given time spaced.

This is the general picture for simultaneous and time spaced vaccines, holding also for HepB (for subgroups) and additional of Pneu. In the large questionnaire study (‘purple’) conducted from January 2005 until December 2007, we saw that the addition of Pneu increased the occurrence of some more severe events a little. The frequency of paracetamol administration was also somewhat higher in children receiving both DTP-IPV-Hib and Pneu (18% versus 27% for dose 4). In addition, we have found no suggestion of increased severity in combined vaccines compared with simultaneous administration for systemic events. For local reactions, this may be so, because combined vaccines have a different formulation (more ingredients/antigens) and may give more irritation and invoke a broader local immune response. This is no rule however. (And again, it means just one local reaction instead of two.)

- Effect of schedule changes, with earlier start at 2 months (from 3 months)

Adverse events depend on the age of the vaccinee. Reactogenicity profiles differ with age. Young infants show other frequencies and types of adverse events compared with older infants and children. This applies for local reactions, less prominent in very young infants, and for fever- also lower and less common. Fever is most prominent in 1-year-olds, sometimes very high. Remarkably, these very-high-temperature reports became more frequent after the introduction of digital thermometers. (Their package inserts note that precision is only guaranteed for temperatures between 37-39 °C, hic.) We once tried to calibrate several different digital household thermometers on 40 °C, resulting in a very divergent and inconsistent useless wide range. Nowadays mercury thermometers are rare. Most parents use digital thermometers and sometimes ear thermometers are used. In the Netherlands, taking rectal temperatures is most common, but sometimes temperatures reported were just by feel or touch. We always add this to the list of choices as to not force parents in choosing an incorrect device. In children 4 years and up, fever is less common and less high.

Crying is also a feature of very young infants, and persistent screaming (PS) follows mainly their first vaccination. PS reports decrease with age and dose number. As said before this applies also for collapse (HHE) and discoloured legs. Febrile convulsions, occur most often in the ~ 1-year- olds (after 4th infant dose and MMR1).
Therefore, acknowledged adverse reactions may be age specific but so are some (background rates of) coincidental events. This applies through life, but especially for infants with rapid succession of physiological states and changes in maturation. Some age specific coincidental events are West Syndrome (WS) and some other severe epilepsies in infancy, manifestation of several metabolic diseases, autism or other developmental problems, as well as stenosis of pylorus, infantile acne, debut of eczema, intussusception, febrile convulsion, fainting, pavor nocturnes, ITP et cetera. Exemplary is SIDS as age specific event. This greatly influences, what adverse events are reported and to be expected. Interpretation is often difficult, and the time interval (lag time) and duration is of great importance for causality assessment. Aggregated results should be compared with background rates as well.

- **Effect of vaccine dose in the series**

In addition to age specific events, dose number plays a role. Generally, the rate of adverse events is greatest after the first dose of a (combined) vaccine. This is true for spontaneous reports and for questionnaire studies. This is not the result of opting out or non-response and not of increased anxiety. Even in randomised controlled trials (RCT) with a 100% follow-up, this showed. It could well be the result of the different (levels of) mediators in first and in subsequent contact with new antigens. (Likewise illustrated in IgM titres after first encounter and (boost in) IgG in following contacts with infectious agents.) Collapse reactions have shown this exemplary. Not only an increase in collapse rate with younger age, but also more collapse, after first doses compared with second doses at the same age.

Vice versa, some events need a first dose or antigen contact to occur, like allergic reactions, which would have to show an increasing frequency with dose number. The local reactions after the 4y booster, appears to be the result of prior immunisation with (specific types of) acellular pertussis vaccine in infancy. Meaningful data for first dose at that age are missing however, by design of the programme nearly all children received vaccines before. Age specific frequencies cannot be compared, therefore. Over time we have checked the rate in children with different infant vaccines; the rate appears to be less for children who received whole-cell vaccine in infancy and may depend on the specific type of acellular pertussis vaccine combination.

- **Effect of transition from whole-cell to acellular pertussis vaccine**

Acellular pertussis combination vaccines are less reactogenic than whole-cell pertussis vaccines, discussed above. This resulted from field trials, but was also apparent in spontaneous reports and questionnaire studies ("green" or "purple"). The latter showed lower frequencies for all solicited adverse events. High fever, vehement crying, went down to 30-20% of previous rates, as did lethargy and irritability. The proportion children getting paracetamol dropped from 49% to 18% for all infant vaccine doses combined, and for dose 4 from 61% to 19%. These questionnaire studies were sequential, but only 1 year apart, with no signal of a changed parental or professional attitude towards paracetamol administration. These questionnaire studies were too small for rare adverse events, for which we rely fully on the passive reports.

For discoloured legs, collapse and febrile convulsions the enhanced passive surveillance system showed to perform well, with limited underreporting over the years. For collapse, for discoloured legs, as well as for febrile convulsions, the reporting rate decreased to approximately 25-30% of the previous levels. However, none of the former adverse events disappeared from the scene. Therefore, relation of these acknowledged adverse reactions with pertussis endotoxin (which is not present in the acellular vaccines) is less likely than always has been assumed. See also under the specific adverse events discussed above, in section 5.2.

As said before, the transition to acellular vaccines had consequences for the 4y booster dose, with an increased rate of prominent local reactions. The trade off in reporting rates
is a decrease for infant vaccinations from 522/100,000 to 385/100,000 vaccinated infants, (26% less) as opposed to an increase from 50/100,000 to 285/100,000 vaccinated 4-year-olds (4-5 times increase). This means fewer infants with 1 or more AE (137/100,000 less) and more 4-year-olds with AE (235/100,000). In doses this is a decrease of reports of 35/100,000 infant doses compared with an increase of 235/100,000 4-year boosters. Mind, this reflects reported adverse events. The impact of adverse events does not rely only on numbers. Age group, type of event, subsequent concern or anxiety, i.e. perception, are also very important.

For expected adverse events following infant vaccines in the Dutch Vaccination Programme, see Appendix 3.

5.3.3 MMR with or without MenC

MMR is a live vaccine introduced in 1987 in 2-dose schedule for all children aged 14 months and 9 years. This replaced single measles vaccination at 14 months and rubella vaccination at 11 years for girls only. The product first used, was MSD’s and later MMR in a slightly different formulation produced by RIVM. During 1 year another brand of MMR has been used simultaneously because of shortage of vaccine (1999–2000). The last few years, two different brands of MMR were used. We have no signals that these changes influenced number or type of reported adverse events. All MMR vaccines appear to have a similar safety profile. Composition is also similar for all products involved. Contraindications are very few, i.e. pregnancy and severe immune deficiencies. Of course, a standard contraindication is allergy for components of the vaccine. So far, we have not come across allergic reactions for components of MMR. Children with allergy for egg-white-protein tolerate MMR vaccine well. This is not surprising, since vaccine viruses are not produced on embryonated eggs but on chick-embryo-fibroblasts (CEF) and a human cell line. In literature, reports have been published from other countries about allergic reactions to gelatine, which we have not seen in the Netherlands, (Europe and North America), perhaps because the gelatine in the vaccine has been hydrolysed. Anyway, this allergic reaction is extremely rare.

The incubation period of (possible) varicella has been rumoured to be contraindicate MMR, but support has not been found. It is also very impractical to keep. We have never followed this alleged contraindication and have no reports on adverse consequences of simultaneous varicella and (risk window of) MMR vaccination.

By the end of the nineties, adverse publicity was generated by a publication in the Lancet of a patient series by Wakefield. 12 children were described with bowel problems and autistic spectrum disorders, which the authors attributed to MMR vaccination. That the author later has been found at fault and having also a conflict of interest, has not resolved the adverse publicity/perception. Harm had been done, and in several countries vaccination rates dropped dramatically, until the present day. Several studies have since then shown that there is absolutely no ground for this allegation. MMR does not cause autism, or inflammatory bowel disease (IBD). It may appear to parents, if autism becomes apparent after the MMR vaccination, that the disorder is caused by the vaccination, even if some months have passed. Sometimes, the children have been rather ill in the risk window for MMR (5-12 days after the vaccination) which they then link to the autism. True, autistic children cope less well with illness and other mishaps than other children do, so this may have been a first sign of the underlying disorder but the MMR is not the cause of the disorder. We have had some reports of autistic spectrum disorder after MMR. In none, the vaccine was considered to be the cause or the trigger. In quite some cases, there were several signals of disturbed communication in late infancy, before the MMR. This does not mean that the cause of autism should be shifted to the infant vaccinations. Several studies show that autism is not linked to pertussis vaccines, with or without thiomersal, either.
The effect of age and dose number on adverse events following MMR

MMR as live vaccine has a 'take or non-take' response. In 90-95% of 1 year old children the vaccination results in replication of vaccine viruses with the intended immune response. After an incubation period of 5 days, adverse effects may develop as well, mostly caused directly or indirectly by the viraemia. The younger the child, the lower the seroconversion rate. This is because of still present maternal antibodies and consequently fewer adverse events. We have no signals that the severity of adverse events in the infant age group is different from that in the regular age group.

Likewise, the second vaccination at 9 years will only affect about 10% of children. This involves the few children that get their first vaccination at this age and those in which one or more of the vaccine strains did not take. It is our experience that adverse events attributable to the 9y-booster MMR are very infrequent.

Effect of adverse events on vaccine coverage

Some parents refuse vaccination, but at least 95% gets MMR before the age of 2 years. At 9 years, the proportion (at least once) vaccinated children is over 97%, resulting in effective herd immunity. Real or perceived adverse events have no great impact on vaccination coverage in the population. Individual parents might opt out after an adverse event following the first dose. For children that were ill after the first vaccination, even if this was fever or rash in the risk window of 5-12 days after vaccination, the second dose is still necessary. First, you cannot be sure that the symptoms are indeed caused by MMR and even if they are, not by which vaccine strain. Moreover, if one of the vaccine strains was the cause, then that specific strain has taken; after the second vaccination, that virus component will be neutralised by the antibodies formed by the first vaccination. In addition, for reactive arthritis after the first dose, for which causal relation with MMR could not be ruled out, the argumentation above applies. The same holds for ITP after the first dose. Antibody tests to decide about the necessity of the second dose, are not advised: they are expensive, cut-off levels for protection are unsure (except for rubella), false positive tests can occur, and tests are unnecessary since in these cases fear for extra adverse events are unfounded (though understandable). In opting for tests, implicitly the risk of vaccination is accentuated and reluctance to vaccinate increases even if for one or more vaccine strains no immunity was found.

If a child experienced a febrile convulsion after the first MMR, there is no risk of recurrence because febrile convulsions do not occur at that age. In addition, if MMR caused the triggering fever at the time, the causative strain has taken and will not replicate again. Most children reported with an adverse event after the first dose, do get their second dose in a routine setting and the course is uneventful.

Effect of addition of MenC vaccine to the schedule

In 2002, after the catch up campaign for children 1-18 years old, MenC vaccination was included in the vaccination schedule. MenC is an inactivated vaccine so the immune response is in the first day for MenC and for MMR between 5-12 days after the vaccinations. The vaccinees get the vaccines together but the immune response is sequential. Adverse events are therefore likely to be sequential too. Most events on the day of vaccination, like fever are not attributable to MMR, but could be caused by MenC. Sometimes rashes on the day of vaccination could be caused by either vaccine and may be altogether coincidental. Local reactions are also quite infrequent in the spontaneous reports. In both the passive surveillance and in the questionnaires of the campaign, reported local reactions were less frequent in the 1-year-olds than in the older children. We very seldom get adverse events reported that are attributable to MenC. In addition, when talking to parents, they hardly ever recall any problems on the first day after vaccination.
The safety surveillance of the MenC campaign of 2002 covered rare, severe or unexpected adverse events, through the enhanced passive surveillance system. In addition, questionnaires surveyed tolerability and special forms monitored immediate adverse events at the vaccination sites. No specific adverse events came up, but some age specific trends showed indeed. Fever was most common in the youngest children and local reactions more common in the adolescents. Reported febrile convulsions occurred, as to be expected in the 1-2 year old children. Fainting was more common in the 9-13-year-olds (Appendix 4B). For the RVP, some 870 children were followed with questionnaires after simultaneous administration of MMR+MenC. 30% reported no symptoms whatsoever in the 2 weeks after the vaccinations. Only 8% reported some local reaction for MenC. Fever (>38 °C) occurred in 2% on day 1 or day 2. Around 10-15% reported crying or other signs of lethargy in the first 2 days. The results affirmed also the expected pattern of adverse events for MMR, with fever in 30% (2% fever>40.5 °C), the peak on day 8-9. Rash had its peak on day 9-10, with in 15% of children having both fever and rash ('vaccinitis'). The reporting rate has increased a little after addition of MenC, involving only few adverse events considered caused by MenC and some increase in coincidental events as well. Most of the increase was for reports of fever and/or rash in the compatible risk window of MMR. This coincided with the public unrest of 2004. The transition to acellular pertussis vaccine curtailed this abruptly for the infant vaccines. For MMR however this continued into 2005 and 2006.

5.3.4 4-year Booster DT-IPV, DTP-IPV

The 4y-booster dose has been followed by a sudden increase in reports, mainly for severe or extreme local reactions. This has been described in literature as well, and linked to acellular pertussis vaccines in infancy. In our series, there has been an indication that this may depend on type of vaccine within the acellular pertussis vaccines. This needs to be further studied with detailed denominators from the vaccination register. If such a link exists, it may shed light on the pathogenesis/physiology of this reaction. The pattern and course of the local reactions do not point to an acute IgE mediated event; it may be a local immune complex reaction based on the local relative concentration of pre-existing antibodies and the injected antigen in the right ratio for complex formation. We have, in reported children, no indication whatsoever for systemic immune complex formation. In the one or two children with prominent local reactions who got a subsequent vaccination nothing untoward happened.

5.3.5 9-year Booster DT-IPV and MMR

Reports after the 9y boosters are infrequent and to a relatively large amount involve syncope and other vasomotor events. Of course local reactions are frequent also but hardly ever bothersome enough to report. No consistent links with some common age specific events have become apparent in the history of the safety surveillance system. Lethargy and malaise at this age may present as headache, unlike in the younger age group. We have no signals that vaccinations cause chronic forms of headache or fatigue syndromes.

5.3.6 HPV

The HPV vaccination campaign in 2009 raised a lot of discussion, concentrating both on effectiveness as well as on (long-term) safety. As a matter of fact this vaccine has been followed longer than most other vaccines in the pre-registration period, because the proof of efficacy can only be detected in the years ahead. The precancerous CIN2 and CIN3 lesions develop late after infection. In the entire follow-up time for efficacy, vaccine safety
was also monitored. No untoward signals have been found. The vaccine has been used in large groups of adolescents and young adults and no severe adverse events have been linked to the vaccine. In the Netherlands, the reporting rate has been very high during the campaign and was a little lower for the HPV in the regular vaccination programme. Most reports concerned vasomotor events, local reactions and some fever or malaise, which is expressed in an age specific way. At this age, it is often headache or tiredness. We have no signals that the vaccine causes chronic headache or fatigue syndromes. Remarkable was the relatively large number of menstrual cycle disturbances reported. These cycle irregularities are frequent in the vaccinated age groups, but apparently, this was interpreted as possibly caused by the vaccination, which targets an infection in part of the uterus.

The HPV campaign has been reported in a separate report as has the first year of HPV in the RVP. [11,72]
6 Conclusion

The reported adverse events following immunisations (AEFI) under the Netherlands Vaccination Programme (RVP) in 2010 were of expected level and type. The decrease in number of reports compared with 2009, was due to settling of public anxiety and professional discussions, fuelled by the 2 large vaccination campaigns. This resulted in fewer consultations and subsequently less reports. The fact that the relative severity and the causality proportion of received reports went up, is a sign that more trivial AE or unrelated were reported less frequently.

The number of reported local reactions after the 4-year booster dose went down, but is still much higher than before 2008. This may be due to some wearing off of the novelty factor after publication and information in the RVP-Newsletter (2008-3 and 2009-8). Time association of this decrease with these publications does not show, whereas change to a different brand of infant acellular pertussis vaccine does coincide with the decreased reporting. The overrepresentation of children with infants hexavalent acellular pertussis vaccine in the reports since this switch seems to point to some causal factor of this vaccine in the occurrence of pronounced local reactions. This needs further clarification.

Nevertheless, despite the decrease in public anxiety, the telephone advisory and consultation service was contacted still around 5000-10000 times. The majority of reports came in by phone, as in other years. This is a much appreciated route of reporting, both by the professionals as well as by the safety surveillance system. It allows real time validation and clarification as well as preliminary assessment of diagnosis and causality likelihood, with discussion of further steps in the processing of the report, like getting an eyewitness account from parents and requesting medical information from GP, hospital or additional data from the child health charts. The most important part of this telephone reporting is often the advice for subsequent vaccinations and the risk of recurrent adverse events. For this advice, experience and data from the safety surveillance are important in the light of the risk perception of professionals and the public. That is why the integral service of reporting and consultation channel is valuable. By splitting this, valuable information and knowledge will be lost. That is why outplacement of the registration of AEFI should not lead to this loss of information and consultation possibilities or loss of quality, nor to inefficient use of resources.

The enhanced passive surveillance system has proven its value, in the high reporting rate as well as in the good quality of data. The name-based reports have allowed validation and supplementation of data as well as follow-up, with possibilities of systematic studies. In the past years, several new insights have been gained through the system. Causality assessment is an important aspect of the safety surveillance. It has implications for the reported individual but also for the risk benefit analysis of the vaccination programme as a whole. It is achieved with the use of available scientific data and will in its turn further enhance the knowledge about adverse events if the summarised homogenous events are studied as a group for lag time, duration and additional or accompanying symptoms.

Periodic questionnaire studies are a valuable tool to monitor tolerability, i.e. common adverse events. The right tool should be chosen addressing the type of specific scientific question. To have all parents report any adverse event will generate a lot of work and spread the sense of unsafety rather than safety. The same applies to giving all parents a web based questionnaire. These tolerability studies should be large enough to supply an answer, but not larger than necessary. For more rare events or new signals the existing wide reporting criteria have served the purpose. The 24 hours available consultation service has contributed to the very high signal receptiveness of the system.
The spontaneous safety surveillance is inefficient for study of frequent AE. It is, however, fit to detect severe, uncommon or peculiar AE, and the possibility to include rare events of special interest via the child health clinics could be explored further. Like wise, the specific monitoring through the Netherlands Paediatric Surveillance Unit, could be used for specific adverse events within the scope of the paediatrician. Parents should primarily contact the providers and/or the GP if they experience an AE or have specific questions about the safety of the vaccinations. This is part of the first line care and guidance of the vaccination programme. For professionals there should be a good accessible high quality consultation service as well as general material to educate and arm them (back them up, support) for the task of the execution of the RVP and to equip them with substantive information to answer parents’ questions and help them overcome their hesitance or reluctance to vaccinate.

Safety surveillance should also be proactive, that is be prepared when new vaccines are introduced/ even before the introduction of new vaccines. Background rates should be collected for possible AE and attention also could be paid to sequential introduction with follow-up of the 2 cohorts. Novel epidemiologic methods are to be explored as well. Preparedness will enhance professional as well as public confidence, and will spread the sense of safety rather than a sense of insecurity. Intensive safety surveillance may detect new signals but an aim is also to underpin the safety of the programme. Several aspects need attention in the coming year:

- Further study of the signal that the 4-year booster local reaction risk is related to type and brand of acellular pertussis vaccines, with the use of detailed denominators from the vaccination register.
- A study on vaccinations and SIDS.
- Questionnaire study on tolerability of the newly introduced universal hexavalent DTP-IPV-Hib-HepB and the 10-valent conjugated pneumococcal vaccine.
- National and international collaboration should be expanded to get quicker results because of the larger numbers and comparison or control groups.
- Further implementation and development of case definitions by the Brighton Collaboration.
- Further case control study on risk factors and follow-up of collapse reactions (COLLAGE).
- Sustaining and stimulation reporting compliance of child health clinic staff, as well as soliciting reports from GPs and paediatricians.
- Publication of study of ITP following MMR and DTP-IPV-Hib (in SCCS design, NSCK).
- Publication of the relation between local reactions after the 4y-booster and type and brands of acellular pertussis infant schedule.
- Publication of the risk of recurrence in discoloured legs.
- Publication of the risk of recurrent collapse reaction after acellular pertussis vaccines, and in the accelerated schedule.
- Publication of the trends in paracetamol administration by parents after RVP vaccinations.

The number of 1380 reported AE should be seen in relation to the over 7 million vaccines given to 800,000 children on more than 1.3 million occasions. The AE should also be balanced against the black number of prevented illnesses and averted complications by these vaccinations. Data show that the vaccination programme is safe and that the benefit of the vaccination programme outweighs the potential side effects by far.
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## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AEFI</td>
<td>Adverse Event Following Immunisation</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacille Calmette Guérin vaccine</td>
</tr>
<tr>
<td>BHS</td>
<td>Breath Holding Spell</td>
</tr>
<tr>
<td>CB</td>
<td>Child Health Clinic (consultatiebureau)</td>
</tr>
<tr>
<td>CBG</td>
<td>Medical Evaluation Board of the Netherlands</td>
</tr>
<tr>
<td>CBS</td>
<td>Statistics Netherlands</td>
</tr>
<tr>
<td>Cib</td>
<td>Centre for Infectious Disease Control (RIVM)</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>DT-IPV</td>
<td>Diphtheria Tetanus Inactivated Polio (vaccine)</td>
</tr>
<tr>
<td>DTP-IPV</td>
<td>Diphtheria Tetanus Pertussis Inactivated Polio (vaccine)</td>
</tr>
<tr>
<td>DTP-IPV-Hib</td>
<td>Diphtheria Tetanus Pertussis Inactivated Polio Haemophilus influenza type B (vaccine)</td>
</tr>
<tr>
<td>DTP-IPV-Hib-HepB</td>
<td>Diphtheria Tetanus Pertussis Inactivated Polio Haemophilus influenza type B Hepatitis B (vaccine)</td>
</tr>
<tr>
<td>ELS</td>
<td>Extended Limb Swelling</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Programme on Immunization</td>
</tr>
<tr>
<td>GGD</td>
<td>Municipal Public Health Department</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>GR</td>
<td>Health Council</td>
</tr>
<tr>
<td>HBIG</td>
<td>Hepatitis B Immunoglobulin</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>HepB</td>
<td>Hepatitis B (vaccine)</td>
</tr>
<tr>
<td>HHE</td>
<td>Hypotonic Hyporesponsive Episode (collapse)</td>
</tr>
<tr>
<td>HPV</td>
<td>Human Papilloma Virus (vaccine)</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IGZ</td>
<td>Inspectorate of Health Care</td>
</tr>
<tr>
<td>IPCI</td>
<td>Interdisciplinary Processing of Clinical Information (database)</td>
</tr>
<tr>
<td>ITP</td>
<td>Idiopathic Thrombocytopenic Purpura</td>
</tr>
<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
</tr>
<tr>
<td>JGZ</td>
<td>Child Health Care</td>
</tr>
<tr>
<td>LAREB</td>
<td>Netherlands Pharmacovigilance Centre</td>
</tr>
<tr>
<td>MA</td>
<td>Medical Consultant of RCP</td>
</tr>
<tr>
<td>MenC</td>
<td>Meningococcal C infection (vaccine)</td>
</tr>
<tr>
<td>MMR</td>
<td>Measles Mumps Rubella (vaccine)</td>
</tr>
<tr>
<td>NSCK</td>
<td>Netherlands Paediatrics Surveillance Unit</td>
</tr>
<tr>
<td>NVI</td>
<td>Netherlands Vaccine Institute</td>
</tr>
<tr>
<td>PCV7/Pneu</td>
<td>7-valent Conjugated Pneumococcal Vaccine</td>
</tr>
<tr>
<td>PMS</td>
<td>Post Marketing Surveillance</td>
</tr>
<tr>
<td>RCP</td>
<td>Regional Coordination Programmes</td>
</tr>
<tr>
<td>RIVM</td>
<td>National Institute for Public Health and Environment</td>
</tr>
<tr>
<td>RVP</td>
<td>National Vaccination Programme</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SCCS</td>
<td>Self Controlled Case Series analysis</td>
</tr>
<tr>
<td>SIDS</td>
<td>Sudden Infant Death Syndrome</td>
</tr>
<tr>
<td>SMEI</td>
<td>Severe Myoclonic Epilepsy in Infancy</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics (package inserts, bijsluiters)</td>
</tr>
<tr>
<td>TBC</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>WWII</td>
<td>Second World War</td>
</tr>
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</table>
Appendix 1: Resume of Product Characteristics 2010

<table>
<thead>
<tr>
<th>Vaccines in RVP</th>
<th>Producer</th>
<th>constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DTP-IPV-Hib vaccine</strong></td>
<td>Aventis Pasteur</td>
<td>Diphtheria toxoid ≥ 30 IE</td>
</tr>
<tr>
<td>Diphtheria, acellular</td>
<td></td>
<td>Tetanus toxoid ≥ 40 IE</td>
</tr>
<tr>
<td>Pertussis, Tetanus and</td>
<td></td>
<td>Pertussis toxoid (PT) 20 μg</td>
</tr>
<tr>
<td>inactivated Poliomyelitis</td>
<td></td>
<td>Filamentous hemagglutinin (FHA) 20 μg</td>
</tr>
<tr>
<td>vaccine mixed with</td>
<td></td>
<td>Fimbriae agglutinogenen 2 and 3 (FIM) 5 μg</td>
</tr>
<tr>
<td>conjugated Hib-vaccine</td>
<td></td>
<td>Pertactin (PRN) 3 μg</td>
</tr>
<tr>
<td>0.5 ml</td>
<td>RVG 32118</td>
<td>Inactivated poliovirus type 1 (Mahoney) 40 DE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inactivated poliovirus type 2 (MEF-1) 8 DE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inactivated poliovirus type 3 (Saukett) 32 DE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Haemophilus influenzae type b polysaccharide 10 μg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conjugated to tetanus toxoid (PRP-T) 20 μg</td>
</tr>
<tr>
<td><strong>DTP-IPV-Hib vaccine</strong></td>
<td>GSK</td>
<td>Diphtheria toxoid* ≥ 30 IE</td>
</tr>
<tr>
<td>Diphtheria, acellular</td>
<td></td>
<td>Tetanus toxoid* ≥ 40 IE</td>
</tr>
<tr>
<td>Pertussis, Tetanus and</td>
<td></td>
<td>Pertussis toxoid (PT)* 25 μg</td>
</tr>
<tr>
<td>inactivated Poliomyelitis</td>
<td></td>
<td>Filamentous hemagglutinin (FHA)* 25 μg</td>
</tr>
<tr>
<td>vaccine mixed with</td>
<td></td>
<td>Pertactin* 8 μg</td>
</tr>
<tr>
<td>conjugated Hib-vaccine</td>
<td></td>
<td>Inactivated poliovirus type 1 40 DE</td>
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<tr>
<td>0.5 ml</td>
<td>RVG 22123</td>
<td>Inactivated poliovirus type 2 8 DE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inactivated poliovirus type 3 32 DE</td>
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<tr>
<td></td>
<td></td>
<td>Haemophilus influenzae type b polysaccharide** 10 μg</td>
</tr>
<tr>
<td></td>
<td>*adsorbed to aluminiumhydroxide 0.95 mg</td>
<td>**conjugated to tetanus toxoid and absorbed to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>aluminium phosphate 1.45 mg</td>
</tr>
<tr>
<td><strong>DTP-IPV-Hib-HepB vaccine</strong></td>
<td>GSK</td>
<td>Diphtheria toxoid** ≥ 30 IE</td>
</tr>
<tr>
<td>Diphtheria, acellular</td>
<td></td>
<td>Tetanus toxoid** ≥ 40 IE</td>
</tr>
<tr>
<td>Pertussis, Tetanus,</td>
<td></td>
<td>Pertussis toxoid (PT) 25 μg</td>
</tr>
<tr>
<td>inactivated Poliomyelitis and</td>
<td></td>
<td>Filamentous hemagglutinin (FHA) 25 μg</td>
</tr>
<tr>
<td>Hepatitis B vaccine mixed</td>
<td></td>
<td>Pertactin* (PRN) 8 μg</td>
</tr>
<tr>
<td>with conjugated Hib-vaccine</td>
<td></td>
<td>Hepatitis-B*** 10 μg</td>
</tr>
<tr>
<td>0.5 ml</td>
<td>EU/1/00/152/001</td>
<td>Inactivated poliovirus type 1 (Mahoney) 40 DE</td>
</tr>
<tr>
<td></td>
<td>EU/1/00/152/002</td>
<td>Inactivated poliovirus type 2 (MEF-1) 8 DE</td>
</tr>
<tr>
<td></td>
<td>EU/1/00/152/003</td>
<td>Inactivated poliovirus type 3 (Saukett) 32 DE</td>
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<tr>
<td></td>
<td>EU/1/00/152/004</td>
<td>Haemophilus influenzae type b polysaccharide*** 10 μg</td>
</tr>
<tr>
<td></td>
<td>*adsorbed to aluminiumhydroxide 0.95 mg</td>
<td>**adsorbed to aluminium phosphate 1.45 mg</td>
</tr>
<tr>
<td></td>
<td>by recombinant DNA techniques</td>
<td></td>
</tr>
<tr>
<td><strong>DTP-IPV vaccine</strong></td>
<td>Sanofi Pasteur</td>
<td>Diphtheria toxoid ≥ 2 IE</td>
</tr>
<tr>
<td>Diphtheria, Acellular</td>
<td></td>
<td>Tetanus toxoid ≥ 20 IE</td>
</tr>
<tr>
<td>Pertussis, Tetanus and</td>
<td></td>
<td>Pertussis toxoid (PT) 2.5 μg</td>
</tr>
<tr>
<td>inactivated Poliomyelitis</td>
<td></td>
<td>Filamentous hemagglutinin (FHA) 5 μg</td>
</tr>
<tr>
<td>vaccine</td>
<td></td>
<td>Fimbriae 2 and 3 (FIM) 5 μg</td>
</tr>
<tr>
<td>0.5 ml</td>
<td>RVG 27569</td>
<td>Pertactin (PRN) 3 μg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inactivated poliovirus type 1 40 DE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inactivated poliovirus type 2 8 DE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inactivated poliovirus type 3 32 DE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>adsorbed to aluminium phosphate 0.33 mg Al</td>
</tr>
<tr>
<td>Vaccine Type</td>
<td>Manufacturer</td>
<td>Components</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>DTP-IPV vaccine</td>
<td>GSK</td>
<td>Diphtheria toxoid*, Tetanus toxoid*, Pertussis toxoid (PT)<em>, FHA</em>, PT*, Pertactin*</td>
</tr>
<tr>
<td></td>
<td>RVG 28912</td>
<td>Inactivated poliovirus type 1, 2, 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*adsorbed to aluminiumhydroxide</td>
</tr>
<tr>
<td>DT-IPV vaccine</td>
<td>NVI</td>
<td>Diphtheria toxoid *, Tetanus toxoid *, Inactivated poliovirus type 1, 2, 3</td>
</tr>
<tr>
<td></td>
<td>RVG 17641</td>
<td>*adsorbed to aluminium phosphate</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>Wyeth</td>
<td>Pneumococcal polysaccharide Serotype 4, 6B, 9V, 14, 18C, 23F, 2, 3</td>
</tr>
<tr>
<td></td>
<td>EU/1/00/167/001</td>
<td>Conjugated CRM197 and absorbed to aluminium phosphate</td>
</tr>
<tr>
<td></td>
<td>RVG 17672</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RVG 22052</td>
<td></td>
</tr>
<tr>
<td>Meningococcal C vaccine</td>
<td>Baxter</td>
<td>Neisseria meningitidis (C14-strain) Polysaccharide (-deacetylated)</td>
</tr>
<tr>
<td></td>
<td>RVG 26343</td>
<td>Conjugated to Tetanus toxoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adsorbed to aluminium hydroxide</td>
</tr>
<tr>
<td>Hepatitis B vaccine</td>
<td>GSK</td>
<td>Hepatitis B-virus surface antigen, recombinant* (HBsAg)</td>
</tr>
<tr>
<td></td>
<td>RVG 24290</td>
<td></td>
</tr>
</tbody>
</table>

**References**

[http://onderzoek.nvi-vaccin.nl/Bijsluiters/Bijsluiters_RVP](http://onderzoek.nvi-vaccin.nl/Bijsluiters/Bijsluiters_RVP)
Rijksvaccinatieprogramma 2010

Opmerkelijke wijzigingen ten opzichte van 2009:
- De vaccinatie tegen Hib-ziekte wordt beperkt tot de 1e jaarlijkse
dosis.
- De voor rijpjaar 2009 aangepaste versies van de HPV-vaccinatie in het RVP is door
omstandigheden uitgesteld tot voorafgaand het vastleg van 2010, en geldt nu voor het hele
geboortestart 1997.

1 Algemeen

1.1 Organisatie
De minister van VWS bepaalt de inhoud van het Rijksvaccinatieprogramma (RVP). In opdracht van
de minister is het RijksCentrum Infectieziektenbestrijding (RIVM) verantwoordelijk voor
de regeling van het programma.

1.2 Vaccinatienota per kind in 2010
Zie het schema hiervan op pagina 2.

1.3 Algemene regels voor toedienen van vaccin
Het toedienen van PEP-vaccin is een medische
handeling. Hiervoor dient altijd een indicatie door
een arts te zijn gesteld.

Appendix 2: Netherlands Vaccination Programme 2010
### Vaccinatieschema per kind in 2010

<table>
<thead>
<tr>
<th>Leeftijd</th>
<th>Vaccinaties (regular)</th>
<th>Vaccinaties (doelgroep HepB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 maanden</td>
<td>DKTR+Hb+1 + PreV-1</td>
<td>HepB-6'</td>
</tr>
<tr>
<td>3 maanden</td>
<td>DKTR+Hb+2 + PreV-2</td>
<td>DKTR+Hb+HepB-3' + PreV-1</td>
</tr>
<tr>
<td>4 maanden</td>
<td>DKTR+Hb+3 + PreV-3</td>
<td>DKTR+Hb+HepB-2' + PreV-2</td>
</tr>
<tr>
<td>11 maanden</td>
<td>DKTR+Hb+4 + PreV-4</td>
<td>DKTR+Hb+HepB-3' + PreV-3</td>
</tr>
<tr>
<td>14 maanden</td>
<td>BMR-1 + MenC</td>
<td>BMR-1 + MenC</td>
</tr>
<tr>
<td>4 jaar</td>
<td>DKTP5</td>
<td>DKTP5</td>
</tr>
<tr>
<td>8 jaar</td>
<td>DTR+ + EMP-2</td>
<td>EPR-1</td>
</tr>
<tr>
<td>12 - 19 jaar</td>
<td>HPV-1 + HPV-2 + HPV-3'</td>
<td>EPR-1</td>
</tr>
</tbody>
</table>

1. Alleen voor kinderen van de doelgroep HepB.
2. Alleen voor de proefafdeling en de doelgroep HepB.
3. Afwijkend voor HepB.

### Schema voor ongevaccineerde kinderen

<table>
<thead>
<tr>
<th>Vaccinatie</th>
<th>Alleen voor kinderen</th>
<th>PreV</th>
<th>tot de 26e verjaardag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMR-1</td>
<td>Autoincidentkinderen op de laadaf van 9 maanden van extra BMR-1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| HepB-6'    | Geboren op of na 1 januari 2009, op voorwaarde dat:
               • ten minste één oudere afkomstig uit een land waar hepatitis B prevalent is en hoewel in Belgische gemeenschappen is.
               • een autoincident kinderen
               • onderschij medische behandeling
               • behandeling van hepatitis B
               • behandeling van HIV
| HPV-1 + HPV-2 + HPV-3' | Geboren op of na 1 juni 2001 |

### 1.5 Registratie en verantwoording

De vaccinaties worden bij het RIVM-RCP door de uitvoerende organisatie verantwoord door inzending van de inpeeldere epepoot; vervolgens registreert en beoordeelt RIVM-RCP de toegelate vaccinaties. Het is voor de uitvoerende organisatie mogelijk de vaccinaties digitale te registreren (RIVVnet).

### 1.6 Financiële regels

De kosten van de uitvoering van het RCP komen ten laste van de AVBZ. De RIVM-RCP’s ontvangen een bestrag per toegelate vaccinatie. De RIVM-RCP’s dragen zorg voor de doorbetalig van de ter beschikking gestelde gelden aan de uitvoerende organisatie volgens landelijke richtlijnen.
1.7 Tijdlijn vaccinaties
Het is van groot belang dat de vaccinaties volgens het geldende schema worden gegeven. Daarom zijn in de lijnplannen alle vaccinaties geïntegreerd met een minimale leeftijd van 6, 7 of 8 maanden. In geval van de Hgb B ondodense in leeftijd ligt de minimale leeftijd na de geboorte aan 1 maand, maar dat is aan te raden als het er is van post-locale reactie er is gebeurde aan een prematuur. De techniek volgt het schema van de vaccinaties van de vaccinaties die er is gebeurde aan een prematuur.

1.8 Vaccinatieinstellingen

1.9 Voorziening
De RIVM/RCP's leveren de vaccinaties aan de vaccinatieinstellingen. De vaccinaties worden gegeven in de vaccinatiezorg eindan de vaccinatiezorg.

2 Toelichting op vaccins en vaccinaties
2.1 Ziektes
DKF (dengue - dengue - febriliteit - febriliteit - poliomyelitis) - Hib tegen melk en melk
Hib tegen melk en melk

2.2 Vaccinaties
DKF (dieet - dieet - dieet - dieet - poliomyelitis) - Hib tegen melk en melk
Hib tegen melk en melk

2.3 Ziektes
DKF (dengue - dengue - febriliteit - febriliteit - poliomyelitis) - Hib tegen melk en melk
Hib tegen melk en melk

2.4 Vaccinaties
DKF (dieet - dieet - dieet - dieet - poliomyelitis) - Hib tegen melk en melk
Hib tegen melk en melk

Bij vaccinaties dient men aandacht te geven aan het vaccinatieplan.

1.10 Aanbevelingen
HepB-0 (tegen hepatitis B)
Voor deze vaccinatie komen kinderen van HbsAg-positieve moeders (draagsters van het hepatitis B-virus) in aanmerking. De verlofduur van het vaccin is 48 uur na de geboorte tot 7 dagen na de geboorte.

DKTP (tegen difterie – kinkhoest – tetanus – poliomyelitis) – Hb (tegen ziekte veroorzaakt door Haemophilus influenzae type b) – HepB (tegen hepatitis B)
Voor deze vaccinatie komen vier groepen kinderen in aanmerking:
1. Kinderen waarvan tenminste één van de ouders afkomstig is uit een land waar hepatitis B middel- of hoog-endemisch is (prevalentie van dragerschap > 7%).
2. Kinderen van HbsAg-positieve moeders (draagsters van het hepatitis B-virus).
4. Asielzoekerskinderen

Ad 1) Deze kinderen krijgen de hepatitis B-vaccinatie op de leeftijd van 2, 3 en 4 maanden in de vorm van het combinatievaccin DKTP-Hib- HepB. Tussen deze drie vaccinaties dient een periode van 4 weken te zitten. De vierde DKTP-Hib-HepB vaccinatie krijgt ze volgens schema op de leeftijd van 11 maanden.

Ad 3) Kinderen van een HepB-vaccinatie waarmee direct na de geboorte is begonnen (zie HepB-0), en voor de onder afz. 1 wordt volgens de schema en de richtlijnen zoals hiervoor vermeld onder afz. 1. Omdat het hier gaat om preventie, dient het schema van 0, 2, 3, 4 en 11 maanden bij deze kinderen eindelijk gevolgd te worden. Om te voorkomen dat het kind bestraft wordt en zelf ook drager wordt, is uitstel van de HepB-vaccinatie niet toegestaan.

Ad 3) Iedereen die de categorie hiervan genoemd onder afz. 1.

Voor alle kinderen met een indicatie voor HepB-vaccinatie is zowel lés HepB-vaccin als het combinatievaccin DKTP-Hib-HepB beschikbaar.

Prene (tegen pneumokokkenziekte)

BMK (tegen bof – maasai – rodehand)
Op de leeftijd van 14 maanden krijgen kinderen de eerste BMK-vaccinatie, Deze vaccinatie wordt simultaan (op dezelfde dag) met de MenC-vaccinatie toegediend, maar in een ander laadkant.

Een asielzoekerskinder krijgt de eerste (extra) vaccinatie op de leeftijd van 9 maanden (BMK-0).

* Wat betekent de prevalentie van dragerschap gaf de WHO een list van landen waar Hepatitis B een-endemisch is, de zogenaamde negatieven landenlijst: Australië, Bahama's, Barbados, BeNeLux, Canada, Chili, Costa Rica, Cuba, Cyprus, Danemark, Duitsland, El Salvador, Estland, Finland, Frankrijk, Hongkong, Irland, Luxemburg, Mexico, Monaco, Nederland, Nieuw-Zeeland, Noorwegen, Oostenrijk, Peru, San Marino, Sri Lanka, Slowakije, Tsjechië, Uruguay, Vatikaan, Veneëgo, Zwitserland. In deze lijst zijn er landen waar de prevalentie van HbsAg is onder de 2% en de WHO geen actiepleging van de landenlijst maar publiceer, blijft de 'oude' landenlijst een bruikbare indicatie geven voor bepaling van de doelgroep voor Hepatitis B vaccinatie.
2.2 Klachten

DKTP (Difterie - Klinthoeve - Tetanus - Polioomyalitis)
De klachten worden niet vaak gevonden. Men wijst de aandacht van de kinderen op de belang van de vaccinatie. Evenals bij andere vaccinaties kan het gebeuren dat er na vaccinatie klachten (zoals koorts, rillingen, soms pijnlijke spieren) optreden. De klachten zijn meestal licht en nemen vaak snel af. De vaccinatie is een veilige en effectieve manier om de kinderen te beschermen tegen deze ziekten.

2.3 Schoolkinderen

DTP (difterie - tetan - poliomyelitis)
Kinderen geboorteklasse 2001 krijgen in 2003 een tweede vaccinatie met DTP-jevel. Bij kinderen in de DTP-klasse is er een lagere risico op klachten en bijna zeker geen gevaarlijke bijwerkingen. Bij kinderen die al eenmaal DTP gevaccineerd zijn, is een tweede vaccinatie niet nodig, tenzij de arts dat raadt.

2.4 Advies houder kinderen

HPV tegen infectie door humane papillomavirus (HPV) en preventie van baarmoeckanker
In 2015 wordt een vaccinatieprogramma toegepast bij kinderen van 11 jaar. Het vaccin is ontworpen als een schijfje ter bescherming tegen HPV en de inderdaad gevonden HPV-verwekkers. De vaccinatie bestaat uit een serie van drie doses die, na een week na elkaar, in de tijd van HPV-actieve schijven, worden gegeven: 11, 12 en 13 jaar. Meestal gaat het om een ongemakkelijke, voornamelijk nachtelijke periodie. De vaccinatie is een veilige en effectieve manier om de kinderen te beschermen tegen deze ziekten.

3 Simultane vaccinaties en registratie van partijnummers
Simultane vaccinaties zijn vaccinaties die op dezelfde dag worden toegepast, in meestal gelijktijdige, maar in principe binnen 24 uur na elkaar. Deze vaccinatie is alleen in geval van andere leden van de gezinslieden plaats te vinden.

Van elke persoon wordt een zorg en letter en schoolhoud vraag en het vragen van vakleser in welk leden van de gezinslieden wordt toegepast. Dit is noodzakelijk voor de herkennings en het vragen van nog andere leden. Bijwerkingen. Door de vaccinatie zijn er bijwerkingen mogelijk. De vaccinatie is een veilige en effectieve manier om de kinderen te beschermen tegen deze ziekten.

4 Bijwerkingen

Natuurlijke vaccinaties kunnen bijwerkingen opleveren. Meestal gaat het om een ongemakkelijke, voornamelijk nachtelijke periodie. De vaccinatie is een veilige en effectieve manier om de kinderen te beschermen tegen deze ziekten.
Informatie RVP

Voor informatie over het Rijksvacinatieprogramma, over de wijze van uitvoering en voor consultatie over individuele kinderen kunt u zich wenden tot het RIVM/RCP in uw wijkgebied.

| RIVM/RCP Noord | Groningen / Friesland / Drenthe | 054-568 8505 | rcpnoord@rwm.nl |
| RIVM/RCP Oost | Overijssel / Gelderland | 0570-481 529 | rcpoost@rwm.nl |
| RIVM/RCP Midden-West | Utrecht / Noord-Holland / Flevoland | 0348-850 040 | rcpmiddenwest@rwm.nl |
| RIVM/RCP Zuid-West | Zeeland / Noord-Brabant / Limburg | 079-348 8218 | rcpzuidwest@rwm.nl |
| RIVM/RCP Zuid | Zeeland / Noord-Brabant / Limburg | 060-232 9111 | rcpsouth@rwm.nl |

Algemene informatie over het Rijksvacinatieprogramma kunt u verkrijgen bij RIVM Centrum Communicatie en Veiligheid, tel. 0348 850 048, of RIVM/RCP Centrale, tel. 030-274 8599.

Voor achtergrondinformation over het Rijksvacinatieprogramma verwijst ik u naar de Uitvoeringsregelen RVP 2010, de VaccinformatieMap en naar de website www.rivm.nl/ntou.

Vragen over de VaccinformatieMap kunt u sturen aan rvpcommunicatie@rwm.nl.

Exemplaren van deze richtlijnen kunt u downloaden van de website www.rivm.nl/ntou of aanvragen bij het RIVM/RCP in uw wijkgebied.

Dr. M.A.E. Coryn-van Speldehouck, arts-epidemioloog, RIVM Programmanagers Centrum Infectieziektenbestrijding.

Bilthoven, december 2009.
Appendix 3A-B: Expected Adverse Events for RVP vaccines

Common expected Adverse Events Netherlands Vaccination Programme

Generally the vaccines are well tolerated. Below the most common adverse events following the infant vaccines. Not everything occurring after vaccinations is caused by these vaccinations. Parents and health care professional should be aware that coincidental illnesses may present after vaccination just by chance and should be diagnosed in time.

A. Adverse events following infant DTP-IPV +/- other vaccines or components

DTP-IPV-Hib and DTP-IPV-Hib-HepB are the vaccines for infants given in a 3+1 schedule at 2, 3, 4 and 11 months of age, with simultaneous conjugated Pneumococcal PCV7 or PCV10 vaccine. The first dose may be given as early as 6 weeks and at least before 9 weeks of age, to assure timely protection for pertussis.

= Local injection site reactions. Frequency depends on cut off level and of course what parents think abnormal or above threshold. These local reactions occur in up to half the infants to some extent, not surprisingly so because when foreign substances are injected in tissue it is normal that the tissue reacts. Moreover the composition is meant to irritate some, because this is a prerequisite for proper immune responses. In fact adjuvants are added for this reason.

Most local reactions are mild and of short duration. Some are more extensive and measure over 10cm in diameter or have a longer duration (less than 1%, from data of questionnaires or RCTs). We get them rarely reported in infants and they are hardly ever the reason for the report. On average 50 reports per year for all infant doses together both for whole-cell and for acellular vaccines; in 30-50% after the 4th dose. The majority involves common inflammation, some persisting nodules which in the end nearly always resolve eventually. Abscess is infrequent, but always possible of course by introducing a pathogen trough the skin. If sterile abscesses do occur with the modern vaccines and formulation is not decided, a negative culture is no proof apart from the fact that cultures often are not taken. Some reported local adverse symptoms are coincidences like a naevus or other local skin condition not present of noticed before. Not always the local reaction is painful in children and sometimes there is only (perceived) pain in infants. A rare condition is the so called “avoidance” in which the child just does not move the leg and sometimes assumes an awkward position, up to a few days of duration, without signs of persistent pain or redness/swelling. The impression is of a lame leg. Needless to say that other conditions need to be rules out if the child is irritable or feverish.

= Fever is a common (con)sequence of vaccinations in infants. This may be occurring in up to 30%, also depending on applied criteria/cut off. The peak occurrence is about 6 hours after vaccination. It is a frequent background symptom, so be aware of coincidental condition and treat fever as a sign more than as an independent symptom. If fever occurs too soon after the vaccination be more aware of something else and realise possible effects of masking by administered paracetamol in the acute phase. Fever caused by the vaccination should not last too long, in majority vaccine related fever lasts less than 1 day. The fever should not be higher on the second day than on the first; this is more suggestive for some coincidental illness. Some children have very high fever, depending also on type and device of measurement. This is rare in the youngest infants but more common in the 1y-olds. Fever of more than 39.5°C occurred in approximately 10% of infants after administration of the 4th dose with whole-cell vaccine within 24h of vaccination. This decreased to approximately 3.5%
following acellular pertussis vaccination. Up to 8 in 1000 had very high fever (≥40.5°C) after the 4th dose in the whole-cell period (within the prior estimation range of 1/100-1/1000). After transition to acellular pertussis vaccines this decreased to 2/1000 vaccinees.

Parents should be advised how to handle fever, not necessarily by paracetamol, and when to seek help. To put the (sick) child in their own bed under duvets is far too warm and on top too soft with a chance to suffocate. It is better to place the child in the room on the firm floor with its own bedding or move themselves to the child’s room floor. We have several reports with serious consequences.

= **Crying** is a common feature in young children and a considerable proportion of infants up to 4 month cry excessively (% depending on case definitions, up to 17%). It is a commonly reported adverse event after vaccination, but here too it is only a sign, not an independent event, so be always aware of an underlying non related cause. Apart from crying at the time of vaccination -which of course is normal but some children are hard to console-, crying occurs often on the day of vaccination. This is most frequent in the youngest infants and sounds very high pitched at that age. The lag time is usually around 3-4h. It often starts suddenly like turning the knob, and stops also rather abrupt in the efforts of the parents comforting. No consistent relation with local reactions has been found. It could probably is a sign and the only outlet for “mammy, I do not feel well at all”. Other consistent relations have been looked for but not found.

Persistent screaming is an unusual long and continuous period of vehement crying, for 3 or more hours on end, for which no specific cause has been elucidated.

= **Lethargy** is a symptom that is expressed differently at different ages. It is quite common following vaccination in infants. In the infant, it could mean more crying, fretfulness, listlessness, lack of appetite, irritability, apathy, tiredness, limpness or weakness et cetera. To be attributed to the vaccination, this should be on the day of vaccination and not last more than one day. A child with persistent screaming, may be listless on the next day as a sign of catch up. But here also, be aware of something else.

= **Drowsiness or sleepiness** was reported in the whole-cell period, for nearly half the children. It is reported after acellular pertussis also, but less frequently. Of course spontaneous reports are not the measure for this, some parents are highly satisfied by this and find it the most elegant side effect, with the child sleeping through it. Indeed if it is the only symptoms there is nothing to be worried about, but here also awareness for something is necessary, just as on a day without vaccination.

= **Vomiting or diarrhoea** is a common feature in infancy. After vaccination it could be indirectly evoked by fever and not necessarily be a result of gastro-enteritis. Direct causation by the vaccination / vaccine constituents is not possible. This event should be treated symptomatically.

= **Discoloured legs** is a syndrome that occurs most often after the 1st vaccine dose. Like collapse it occurs 3-4 hours after vaccination. Typically it is accompanied by intense crying for a few minutes to sometimes several hours. Discolouration is blue, red or purple and may be even or patchy. It is not located at the injection site but the injection site may be included. The extension may be the entire leg, sometimes including the pelvis from belly button downwards with inclusion of the toes. The discoloration may also be just the feet or lower legs, or even the knees only. Often the discoloration is both sided even if only one vaccine has been administered. It may also be only heterolateral and not on the side of the vaccination. The duration is from a few minutes to several hours/the rest of the day. Some children develop after resolution of the discoloration, petechiae on the leg, sometimes noticed the following morning. This
may also occur without noted prior discoloration. This event sometimes recurs after a subsequent vaccination but usually it does not.

- **Collapse reaction** is an acknowledged adverse reaction. They typically occur 3-4hrs after vaccination and consist of the triad pallor, limpness and reduced conscious. It scares eyewitnesses very much. It typically occurs after the first vaccinations, has a small risk of recurrence and does not leave any defects or harm. It is considered a vasomotor event, not a central neurological event. See for further details under this specific event above. In the Netherlands the near absolute contra-indication had been abandoned in 1994, and since then proven to be the right choice, followed up by WHO. The rate was 1/1000-2000 vaccinees after whole-cell vaccinations and has been reduced to about one third. The chance of recurrence is low, 1-4% and if the events recurs it is also without permanent effects.

- **Convulsions**, mainly febrile, are common in young children. 2-5% of children experience febrile convulsions in their life in the age between 6m and 4-5y, with a peak in the 1y-olds. No wonder that this is an acknowledged adverse event after DTP-IPV (+/-) vaccination (and after MMR). The pattern is not different from convulsions provoked by another cause of fever nor is the prognosis. It should been seen as a sign of the underlying predisposition and not a consequence of a specific vaccine component, but as a result of the fever(pattern). It often is the first or only episode the child will have so for parents it may be very unexpected and frightful. Like other febrile convulsions it could also be a symptomatic convulsion of another disease or the first seizure, triggered by fever, of an underlying epilepsy. So here applies also to be aware of other diseases. Typically the febrile convulsion after (fever by) the vaccination is in the first evening or night after the vaccination, at least within 24h. If they occur later, than another cause is much more likely. Convulsions without fever are more rare and only if occurring within 24h, the vaccine as non-specific trigger cannot be ruled out as cause. These children should be followed up for an underlying disease.

- **Allergic reactions** are very rare if they occur at all. In the history of safety surveillance at RIVM we have never had an proven allergic reaction reported. Positive skin tests are not predictable and should therefore not be performed. In addition, the adjuvant in the vaccine poses a risk of ulceration if injected intradermally. In children with urticaria with or without other symptoms, it has been proven that the schedule can be continued without risk. Most of the time nothing untoward happens after the next vaccination and at worst, there is a repeat of urticarial rash.

- **Eczema** sometimes worsens after vaccination of has its debut. This is not to be interpreted as sign of an allergy to a vaccine component, but may be the result of non-specific immune stimulation. It has been known to happen that eczema improves for some time after vaccination also. Parents tend not to complain about this however. The effect of vaccination is not lasting and vaccination does not influence the natural course of the disease. After advancement of the schedule eczema follows the first dose more often compared with the first dose at 3 months of age. This is not because of the vaccine, but because often the first appearance of eczema is somewhere between 2 and 3 months of age.

If rare or unexpected events follow the infant vaccinations these should be reported as adverse events. Also severe or extreme acknowledged adverse events should be reported, since only then is it possible to keep track of trends or detect new events. In addition any event after vaccination is considered severe, if it leads to deferral of further vaccinations; that applies similarly to events causing public anxiety.
In the reports we have several cases of delay in diagnosis and treatment in coincidental severe infection or other severe illness, with all consequences, because the vaccination was regarded as the (only possible) cause. The vaccination should always be in the differential diagnosis, nothing less but certainly nothing more!

B. Adverse events following MMR1 and MenC vaccinations

- Fever may occur on the day of vaccination (day 0) but is quite uncommon after MenC, so be aware of a different cause, especially is the child is irritable, looks ashen or is apathetic. MMR cannot be the cause of fever on day 0. Fever on day 1 till day 4 (inclusive) is not vaccine related. Fever caused by MMR must occur at least 5 days after and not later than on day 12. Some children have very high fever (≥40.5°C) with or without a rash. Fever with or without rash is the most reported event in the passive system after MMR and MenC vaccination, covering around 40% of reports of which one third with very high fever (≥40.5°C). and rashes account for 12%, together about half the reports, of which about 70% is considered causally related 30% concerns coincidental rashes or rash illnesses. Convulsions account for 25% of the reports in 75% related to mainly the MMR vaccination.
Appendix 4A-E: Poster copies

Appendix 4A

**Recurrence of Collapses (Hypotonic-Hyporesponsive Episode, HHE)**
after infant whole cell pertussis vaccination
in the accelerated schedule of the Netherlands; Follow up study

**Introduction**
- Collapse or HHE occurs in 1/1000-2000 children after infant whole cell pertussis vaccination.
- Collapse is most frequent after the first dose.
- Collapses reported were identical to those reported in the routine surveillance.
- Since the contraindication was applied less often and by 1999 it has been fully reversed in the Netherlands.
- Recurrent collapse after pertussis vaccine was rare (0-23) in 1984-95†" 1984-95:802-3
- In 1999, because of increased pertussis, the 3rd vaccine dose was administered at 2 months of age.
- Since 1999 recurrent collapse has been reported more often than before.
- Preliminary estimates from routine follow up at RIVM suggested recurrence rate of 4.2%
- The rate of recurrence was re-estimated in the same design as in 1994-95, in 1 birth cohort, 2000-2003.

**Reporting Criteria**
- Adverse Event Following Immunisation (AEFI)
  - Severe events
  - Unexpected or persistent events
  - Events (potentially) leading to public unrest

**Case definitions of Collapse**
- Violent, convulsions, unconsciousness
- Improved adaptively sometimes hypotonia of myoclonic seizure
- Loss of consciousness

**Reported Collapses Cohort 1996-2003 (Birth cohort: approx 30,000 births and coverage 87%)**

**Vaccination Schedule of the Netherlands 1984-2007**

**Enhanced Passively surveillance system**
- Vaccination procedure fully extended to Child Health care
- High reporting rates by clinic staff, with full name and address
- Outcome validation and supplementation of data by RIVM
- Reporting system
- Diagnoses according to case definitions by RIVM
- Routine follow up of subsequent doses
- Determinations available from vaccination register
- Reporting forms with 24-hour telephone service for consultations
- Wide area restricted reporting criteria

**Conclusion**
- Collapses appear to be age and dose specific.
- Younger age leads to more collapse reactions.
- The rate of recurrent collapse is also somewhat larger in the accelerated schedule.
- Only follow-ups of subsequent doses were apparent.
- No need for contraindication in recurrent collapse.

RIVM National Institute for Public Health and the Environment, PO Box 1, 3700 BA Bilthoven, the Netherlands. www.rivm.nl
Idiopathic Thrombocytopenic Purpura (ITP) following MMR vaccination; Netherlands Paediatric Surveillance Unit (NSCK) reports analysis in self controlled case series design (SCCS)

Introduction
- ITP in childhood usually follows some nonspecific viral infections
- It is known to occur after MMR vaccination and possibly other vaccinations
- Recovery is the rule
- Complications and sequelae are rare
- Reporting to enhanced passive surveillance of the vaccination programme is incomplete in the Netherlands
- Risk estimates of ITP after MMR are not available in the Netherlands
- Risk estimates were calculated on sentinel reports through NRZA
- NSCK covers 90% of paediatrics in the Netherlands

Case only design analysis of reported ITP 2002-2003
- Incident cases in 2002-2003 were reported through NRZA
- Questionnaires were supplied upon reporting to the paediatrician
- A list of questionnaires were returned to NRZA, with support as needed
- Subsequent linkage to vaccination data from the Vaccination Register
- Exchange between new reports, as well as laboratory data
- Vaccination data were retrieved from the Vaccination Register
- Data were collected through Child Health Clinics, Parents or GPs
- Follow-up continued until patients had recovered (except 3.2-yr post diagnosis)
- Data analysis via self-controlled case series design (SCCS) patients reporting with event-dependent exposure and risk window 6 weeks after MMR-1

Case definition of acute ITP
- Platelet count < 50 x 10^9/L
- Symptomatic bleeding tendency
- Recovery within 12 months and platelets remaining > 50 x 10^9/L

ITP per 6-week periods before and after MMR-1 vaccination

ITP following MMR-1 in 2002-2003
- 41 cases
- 12-24 months old
- 2 ITP within 42 days after MMR-1
- 9 ITP 0-6 weeks before MMR-1

ITP following MMR-1 within 6 weeks
- Relative incidence: 0.8 (95% CI: 3.7-12.2)
- Absolute risk ITP: 1.45 per 10^4
-Attributable risk: 2.22 per 10^4 MMR-1

Conclusion
- Increased risk of ITP after MMR-1
- Risk somewhat higher than in other studies
- No indication of selective reporting
- ITP after MMR-1 follows a relatively mild and short course
- No child with ITP before MMR-1 had a recurrence after MMR
- Up to date on child with ITP after MMR-1 had a recurrence after MMR-2
- ITP after MMR-1 is much less frequent than after natural infection with IBV or Mosquitoes

* Evidence (Q104C4T10500-N1132)

RIVM National Institute for Public Health and the Environment, PO Box 1, 3720 BA Bilthoven, the Netherlands, www.rivm.nl
Paracetamol for Adverse Events after Pertussis immunisation in infancy in the Netherlands

Prophylactic or therapeutic use, whole cell versus acellular pertussis vaccines

Background
- Enhanced post-vaccination surveillance system at RIVM
- Very adequate coverage in paediatric routine for specific AE
- Supplemented systematic studies for vaccine-related, secondary vaccination and vaccination programmes
- Surveillance of adverse events, severe and uncommon
- Medical intervention: treatment and intervention ratios
- OB and confidence intervals for proportions and their differences
- Data is acquired from ACV, ACVH, ACVH, Dep boiler and ACVH
- More detailed description of methods in Vaccines 2006; 26: 983-17

Results
- Response rate 549, age range 1790 and age range 71727
- Acknowledged Solicited AEs: for whole cell 10.2%
- 55% male and 45% male, no differences in reported AEs or medication between sexes
- Proportion of medication with AEs: 10.4 (4.2-2.4)
- AEs: Fever, chills, redness, increase in specific AE: 0.8-1.5 (0.4-1.4)
- Proportion of medication in therapeutic (AE: 0.4-1.6)
- Exclusion: increase in therapeutic medication; index = 0.4-1.6
- Exclusion: increase in therapeutic medication; index = 0.4-1.6
- not only due to increase of dose 4 in this subgroup

Solicited Adverse Events in the questionnaire
1. decrease in appetite 1.34 days, within 24 hours
2. fever 1.34 days, within 24 hours
3. pain, within 24 hours
4. red or jaundice, within 48 hours
5. rest of paracetamol before or after vaccination

Table 1: Prophylactic or therapeutic use at each vaccine dose. Wt vs. AEs: whole cell or plus F皎

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Prophylactic</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>wt</td>
<td>dose %</td>
<td>dose %</td>
</tr>
<tr>
<td>800</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>800</td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td>800</td>
<td>18%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Conclusions
- Decreased use of paracetamol since the transition to acellular pertussis vaccination in infancy
- Since introduction of acellular vaccine, the same incidence in paracetamol use
- No differences in solicited adverse events between male and female, nor in paracetamol use
- Estimated number of paracetamol doses for wt schedule at least 350/600 per year and at least 220/500 for all schedule
- Trade-off between preventability of infant vaccination with subsequent coverage and side effects of paracetamol: what is the balance?
- Paracetamol may mask constitutional events following vaccinations, with possible delay in true recognition and management
- Further education of parents warranted, especially with regard to the management of fever, eg cold bathing and wet sponging
- Improvement in trial procedures of vaccine administration in order to diminish local reactions and pain

RIVM: National Institute for Public Health and the Environment, PO Box 1, 3730 BA Bilthoven, the Netherlands, www.rivm.nl
Appendix 4D

Syncope in mass vaccination campaigns in the Netherlands
MenC in 2002, HPV in 2009, H1N1 in 2009

Vaccination Campaigns in the Netherlands
- 2002 Meningooccal C (MenC) for children in 11-14 y
- 2005-2007 HPV 3 doses (HPV for girls 11y)
- 2006-2008 Pneumococcal (Hib) for children 2-5 y
- 2008-2009 Rotavirus vaccine for children 2-5 y
- 2009 Diarrhoea and RTIs in infants
- 2009-2010 Flu vaccine for children 2-5 y

Questionnaires for Immediate Adverse Events Monitoring (iMAE)
- Distributed to all vaccination sites
- Filled in by Provincial Health Staff and sent to RIVM
- Typing of immediate adverse event, severity, legible, duration, causality, management, and outcome
- Date and time of vaccination
- Dose number and batch number of vaccine
- Name, age, and sex of vaccine
- Total number of administered vaccines per site
- Circumstances, location, and other environmental factors

Denominators from vaccination registers
- MenC from specific regional MenC register
- HPV from the National Vaccination Programme Register
- Influenza from a special province’s register

Results
- Reported iMAE followed most frequently dose
- Occurrence with passive reporting and stringency studies
- Events were the most frequent reported iMAE (14-56%)
- Occurrence was variable and appeared to be dependent on type of event and age
- Events were reported significantly in pre-adolescents
- Injury occurred in up to 40% of events
- Events were accompanied by nausea, vomiting, rash, or pain
- Frequency of concordant symptoms seems age-dependent
- No anaphylaxis was observed

Conclusion
- Reports and syncope occur in the early school years in mass vaccination settings
- Up to 1% of events result in injury
- Package information to address boys and adolescents

Table 1: Comparison of the three vaccination campaigns for immediate adverse events (iMAE)

<table>
<thead>
<tr>
<th>Target group</th>
<th>HPV</th>
<th>MenC</th>
<th>H1N1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td>11-14 y</td>
<td>11-18 y</td>
<td>5-16 y + parents of young infants</td>
</tr>
<tr>
<td>Campaign Coverage</td>
<td>93%</td>
<td>90%</td>
<td>71%</td>
</tr>
<tr>
<td>Schedule</td>
<td>1 dose</td>
<td>2 doses</td>
<td>2 doses</td>
</tr>
<tr>
<td>Vaccinated (N)</td>
<td>1,873,516 (62%)</td>
<td>1,873,516 (99%)</td>
<td>830,038 (21%)</td>
</tr>
<tr>
<td>Attended doses</td>
<td>1,873,516</td>
<td>1,873,516</td>
<td>830,038</td>
</tr>
<tr>
<td>Any mild/10,000 vaccines (any dose)</td>
<td>23</td>
<td>77</td>
<td>6</td>
</tr>
<tr>
<td>Any mild/10,000 vaccines (any dose)</td>
<td>23</td>
<td>77</td>
<td>6</td>
</tr>
<tr>
<td>Minor reaction/10,000 vaccines (dose 1)</td>
<td>2.1 (4/1,873,516)</td>
<td>20.5 (20.5/1,873,516)</td>
<td>26.0 (26.0/830,038)</td>
</tr>
<tr>
<td>Major reaction/10,000 vaccines (any dose)</td>
<td>2.8 (23/1,873,516)</td>
<td>68 (68/830,038)</td>
<td>91.4 (91.4/830,038)</td>
</tr>
</tbody>
</table>

Authors: Patricia E. Vermeer en Boss, Texas A. van’t Hof, Maarten J. van Rooyen, van de Wijga, et al.
Centre for Infectious Disease Control-Gid

Contact: patricia.Vermeer@rivm.nl

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Appendix 4E

Increased risk of local reactions after booster DTaP-IPV in the Netherlands
association with transition to infant acellular pertussis vaccine

Background
- Acellular pertussis vaccine was added to the 3-years-old booster DTaP-IPV since autumn 1996.
- Immunisation schedule (4 doses) shifted from whole-cell to acellular pertussis combination vaccines in 2005.
- In 2007 reports of local reactions with high fever suddenly increased.
- Types and brands of vaccines have differed, both for infants and for boosters.
- Our interest is the effect of a risk of adverse events (AE) after the 4th booster

Methods
- Reports (vaccination over 1995-2006 for 1996-2005 cohorts) were categorized using the standardised criteria for diagnosis consult all reports, www.rivm.nl.
- Coverage denominators (date, age, vaccine dose, vaccine type) were available from the National Vaccination Register

Vaccination Schedule and vaccines for infants and 4 years olds over the years

<table>
<thead>
<tr>
<th>Year</th>
<th>Infant 4 doses</th>
<th>6 years booster</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>DTP-IPV-Hib-Hept</td>
<td>DTaP-IPV-Hib-Hept</td>
<td>INF-HEP-HEP</td>
</tr>
<tr>
<td>2003</td>
<td>DTP-IPV-Hib-Hept</td>
<td>DTaP-IPV-Hib-Hept</td>
<td>INF-HEP-HEP</td>
</tr>
<tr>
<td>2004</td>
<td>DTP-IPV-Hib-Hept</td>
<td>DTaP-IPV-Hib-Hept</td>
<td>INF-HEP-HEP</td>
</tr>
<tr>
<td>2005</td>
<td>DTP-IPV-Hib-Hept</td>
<td>DTaP-IPV-Hib-Hept</td>
<td>INF-HEP-HEP</td>
</tr>
<tr>
<td>2006</td>
<td>DTP-IPV-Hib-Hept</td>
<td>DTaP-IPV-Hib-Hept</td>
<td>INF-HEP-HEP</td>
</tr>
</tbody>
</table>

Conclusions
- The increase in reported severe or extreme local reactions after booster with DTaP-IPV in 6 years of age was related to the transition to acellular vaccines for infants.
- Reporting rates have increased from approximately 1 case per 100,000 doses to 1 case per 50,000 doses over the years.
- Some indications found that the occurrence of reported local reactions might be influenced by specific acellular vaccines in the 4th booster schedule.
- Further validation and clarification of this signal is warranted, not so much because of clinical relevance, but because it might shed light on the pathogenesis.
- Attention should be paid to proper management of local reactions.
- A definitive association of local reactions with previous local reactions or with the acellular pertussis booster requires further evaluation, in order to reduce observation of any further reactions.