National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

Adverse Events in the Netherlands

Adverse Events in the Netherlands Vaccination Programme

Reports in 2010 and Review 1994-2010

National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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

Colophon

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

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 ($\geq$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
Intensieve veiligheidsbewaking is sinds 1962 een vast en noodzakelijk onderdeel van het vaccinatieprogramma. Vanaf 1983 is jaarlijks hierover gerapporteerd, waarbij een onafhankelijke partij meldingen herbeoordeeld. Het gestimuleerde bewakingssysteem heeft een uitermate hoge meldgraad en is door de jaren heen steeds gevoelig gebleken voor signalen. Het laat bovendien toe dat meldingen op langere termijn worden gevolgd, omdat bijwerkingen op naam worden gemeld. In dit laatste jaar van de veiligheidsbewaking bij het RIVM wordt naast de meldingen van 2010 een overzicht gegeven van bevindingen vanaf 1994. Dit toont diverse nieuwe inzichten.

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, collapsreacties, verkleurde benen, koortsstuipen 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

Contents

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

De bijwerkingenbewaking van het Rijksvaccinatieprogramma is door het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) verzorgd sinds 1962. Van 1984 tot 2003 werd hierbij nauw samengewerkt met de Gezondheidsraad (GR) die jaarlijks over een selectie van de meldingen rapporteerde. Vanaf 2004 werd de onafhankelijke herbeoordeling van complexe of ernstige vermoede bijwerkingen voortgezet door een door het RIVM aangezochte groep experts. De telefonische informatiedienst voor consultatie en advies is een belangrijk instrument in deze gestimuleerde veiligheidsbewaking gebleken. Het RIVM rapporteert sinds 1994 jaarlijks over alle binnengekomen meldingen, onafhankelijk van het oorzakelijke verband. Dit rapport over 2010 is het zeventiende jaarrapport. Het zal tevens het laatste rapport in de serie zijn omdat de bijwerkingenregistratie sinds 1 januari 2011 is overgegaan naar Lareb. Om die reden zal in dit laatste rapport ook een overzicht zijn opgenomen over de periode 1994-2010.

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 ziekenhuisspecialisten 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 casusdefinities 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 elkaar 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 zogenoemde 'minor' lokale of algemene ziektebeelden geclassificeerd, waarvan er 540 (73%) een mogelijk oorzakelijk verband hadden. Zogenoemde '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 (achterademhuilen 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 veroorzaakten 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

Age	Vaccine		
birth	HepB0[a]		
2 months	DTP-IPV-Hib1(-HepB[b])	+	Pneu 1
3 months	DTP-IPV-Hib2(-HepB[b])	+	Pneu 2
4 months	DTP-IPV-Hib3(-HepB[b])	+	Pneu 3
11 months	DTP-IPV-Hib4(-HepB[b])	+	Pneu 4
14 months	MMR1	+	MenC
4 years	DTP-IPV5		
9 years	DT-IPV6	+	MMR2
12-13 years	HPV dose 1,2,3	girls only	

[a] =   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).[3] 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. [13,14]
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. [15]
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. [14]
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. [16]

Requirements for post marketing surveillance (PMS) of adverse events have been stipulated in Dutch and European guidelines and legislation. [17,18] 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. [19] The WHO keeps a register of adverse reactions as part of the global drug-monitoring programme. [20] 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. [21,22]

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. [23,24,25,26] 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. [27,28] Not only true side effects but also events with only temporal association with vaccination may jeopardise the uptake of the vaccination programme. [29] This has been exemplified in Sweden, in the United Kingdom and in Japan, in the seventies and eighties 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. [30] In addition, recently concerns about safety rather than actual causal associations caused cessation of the hepatitis B programme in France. [31,32] 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. [27,33,34,35,36,37] Subsequent (local) measles epidemics have occurred and are occurring as we speak, in Europe. [38,39,40]

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. [41,42,43,44,45,46,47,48] 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. [49]

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.[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:

o   *Vaccine*: immuno-biologic product for active immunisation against infectious diseases.
o   *Vaccination*: all activities necessary for vaccine administration.
o   *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.
o   *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. [50,51,52,53]

Box 2   Origin / subdivision of adverse events by mechanism

- Vaccine or vaccination intrinsic reactions	are caused by vaccine constituents or by vaccination procedures; i.e. fever, local inflammation and crying.
- Vaccine or vaccination potentiated events	are brought about in children with a special predisposition or risk factor; for instance, febrile convulsions.
- Programmatic errors	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.
- Chance occurrences or coincidental events	have temporal relationship with the vaccination but no causal relation; these events are of course most variable and tend to be age-specific common events.

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

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

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 $\geq$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. Durante 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).

o   *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.

o   *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 ≥40.5 ºC, autism, diabetes, ITP, severe infections, et cetera. [59,60,61]

o *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]

o *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]

o *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]

o *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 limpness and accompanied by vasomotor symptoms, occurring in older children.

o *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 ≤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

o *Encephalitis /encephalopathy*
Events booked here are considered major. A child <24 months with encephalopathy has loss of consciousness for ≥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]

o *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]

o 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

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

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. [44] 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. [45] 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. [11] 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. [69,70] 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

year of notification	number of reports	birth cohort
1994	712	195,611
1995	800	190,513
1996	732	189,521
1997	822	192,443
1998	1100	199,408
1999	1197	200,445
2000	1142	206,619
2001	1331	202,603
2002	1332	202,083
2003	1374	200,297
2004	2141	194,007
2005	1036	187,910
2006	1159	185,057
2007	995	181,336
2008	1290	184,634
2009	1647	184,824
2010	1380	183,366

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%. [14] 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.
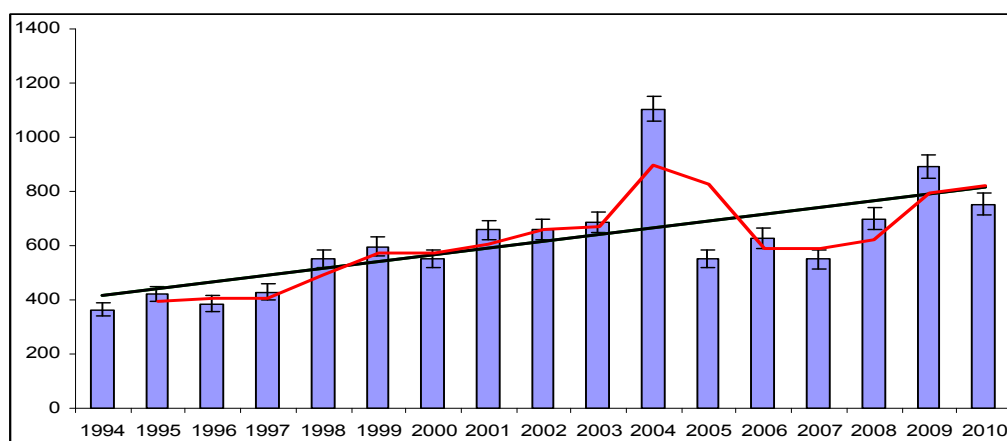
Figure 1   Reporting rate per 100,000 vaccinated infants for AEFI for 1994-2010, with moving average and trend line

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

Reports	children 2010 [a]	Reported AE 2010	AE 2009	AE 2008	AE 2007	AE 2006	AE 2005	AE 2004
single	1158	1158	1404	1161	837	967	890	1756
multiple	58 [b]	122	151	60	107	116	99	280
compound	37 [c]	76	86	50	44	66	44	80
compound and multiple	7	24	6	19	7	10	3	25
Total 2010	1260	1380	1647	1290	995	1159	1036	2141

[a] 25 children had also reports in previous years; these are not included
[b] 6 children with triple reports
[c] 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.
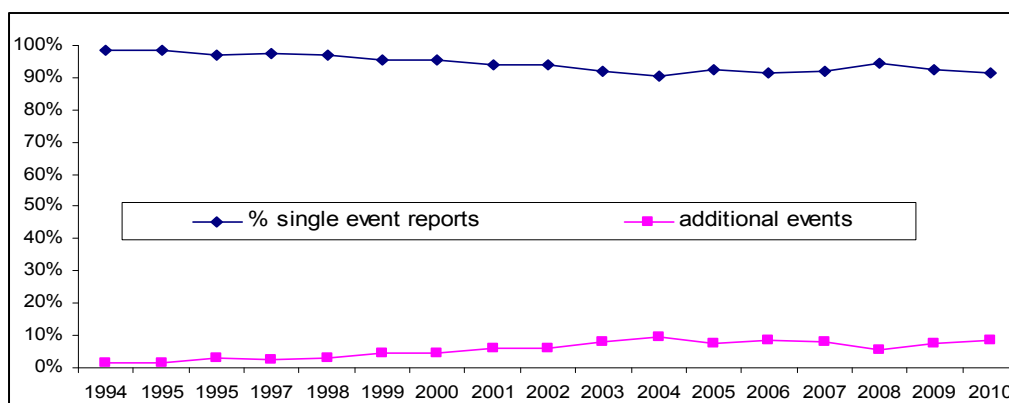
Figure 2   Proportion of single event reports for 1994-2010 with proportion of additional events (multiple or compound)

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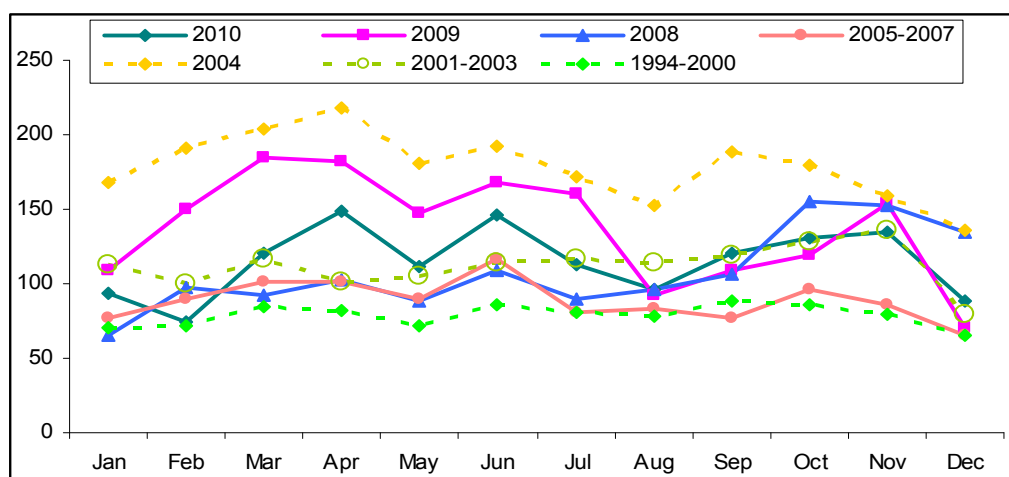
Figure 3   Absolute numbers of reports per month for 1994-2010; reports for whole-cell pertussis DTP-IPV-Hib are in dashed lines

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 break down 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).
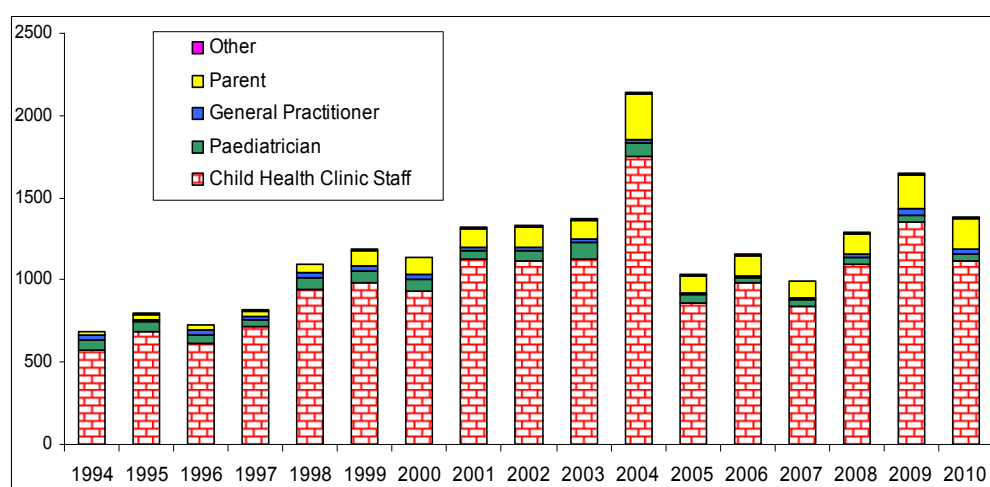
Figure 4   Reporters of AEFI under the RVP for 1994-2010

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*

		2010	phone %	2009	2008	2007	2006	2005	2004
Child Health Care	Child health clinic	991	91,3%	1271	1010	777	894	775	1685
	Municipal health service	107	27,1%	51	81	50	80	76	44
	District Consultant	14	78,6%	28	9	18	8	12	21
Paediatrician		47	85,1%	46	35	33	35	48	84
General Practitioner		27	88,9%	35	23	15	11	13	24
Parent		197	77,6%	206	125	98	121	102	271
Other		2	100%	10	7	4	10	10	12
Total		1380	84,1%	1647	1290	995	1159	1036	2141
(% written reports)			(16)	(13.2)	(8.1)	(7.8)	(9.6)	(11.3)	(12.9)

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.
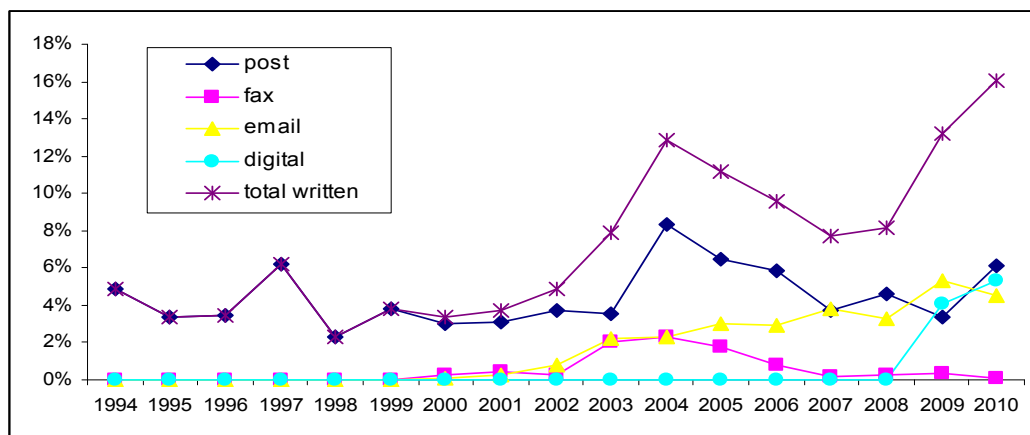
Figure 5A   Route of incoming written reports in AEFI for 1994-2010
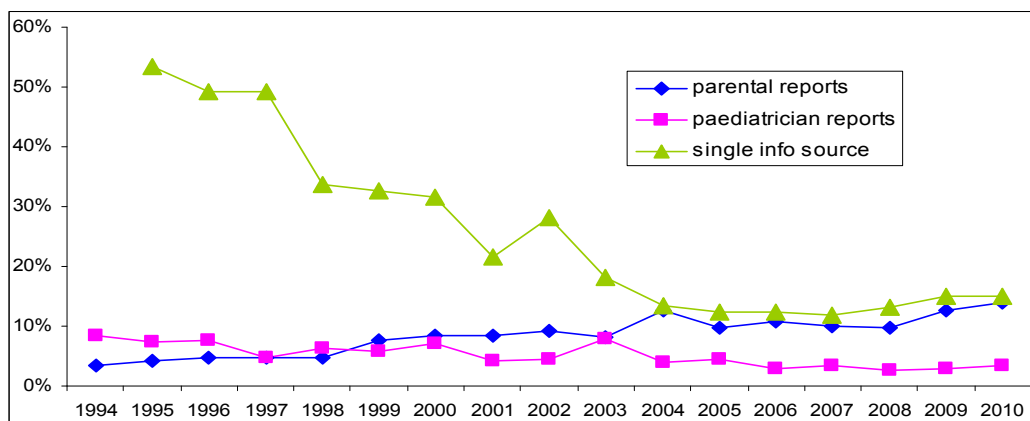
Figure 5B   Reporters, routes, single information source in reported AEFI for 1994-2010

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.
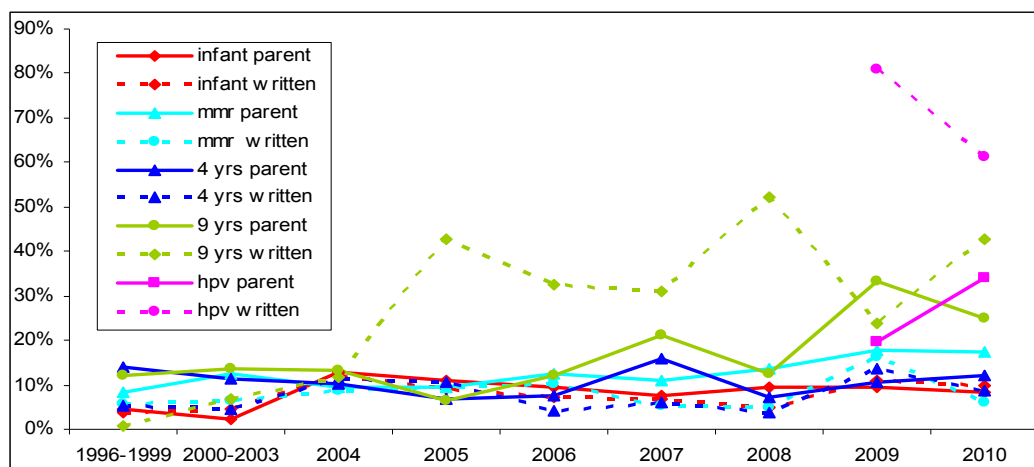
Figure 6   Proportion major events in parental reports and written notifications per vaccine dose in 1996-2010 (HPV all doses)

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).

	2010 (major)	95% CI 2010 (major)	2009 (major)	2008 (major)	2007 (major)	2006 (major)	2005 (major)	2004 (major)
Groningen	6.2 (4.0)	4.3-8.5 (2.6-5.9)	8.6 (4.3)	6.3 (3.4)	5.1 (2.4)	7.4 (3.8)	6.7 (2.5)	16.4 (9.8)
Friesland	9.1 (5.0)	7.1-11.6 (3.5-6.9)	8.4 (2.4)	6.9 (3.4)	4.3 (2.4)	5.9 (3.1)	5.1 (3.0)	13.1 (7.7)
Drenthe	4.4 (2.6)	2.8-6.6 (1.4-4.3)	8.7 (4.1)	3.3 (1.6)	2.6 (1.4)	5.4 (2.7)	5.3 (2.7)	12.6 (10.1)
Overijssel	7.7 (2.5)	6.3-9.4 (1.8-3.5)	11.6 (4.4)	8.3 (3.7)	6.3 (2.9)	7.0 (3.5)	4.2 (1.6)	11.2 (5.8)
Flevoland	9.7 (4.1)	7.2-12.7 (2.6-6.2)	10.2 (4.1)	7.6 (2.5)	4.9 (1.4)	6.1 (2.5)	8.7 (3.7)	16.3 (9.1)
Gelderland	7.4 (3.2)	6.6-9.0 (2.5-4.0)	9.6 (3.6)	6.6 (2.5)	6.0 (2.6)	6.0 (2.9)	5.8 (2.4)	10.8 (5.8)
Utrecht	9.4 (3.6)	7.9-11.0 (2.7-4.6)	11.1 (4.9)	9.9 (5.7)	7.3 (3.2)	8.6 (5.5)	8.1 (4.6)	8.1 (4.9)
Noord-Holland [c]	9.7 (3.9)	8.4-11.1 (3.1-4.9)	8.8 (3.2)	6.5 (2.4)	4.9 (1.8)	5.8 (3.2)	5.0 (2.5)	9.3 (5.2)
Amsterdam	7.6 (4.3)	5.9-9.6 (3.1-5.9)	6.6 (2.4)	9.5 (4.3)	4.6 (1.8)	6.9 (3.6)	5.4 (2.1)	9.8 (4.1)
Zuid-Holland [c]	7.5 (3.1)	6.5-8.6 (2.5-3.8)	9.9 (3.6)	7.2 (3.7)	5.9 (2.5)	6.6 (2.9)	5.2 (2.5)	11.8 (6.4)
Rotterdam	2.7 (2.1)	1.7-4.2 (1.2-3.5)	3.6 (1.4)	5.0 (2.3)	3.0 (1.4)	4.5 (2.0)	3.7 (1.9)	6.6 (4.7)
Den Haag	10.6 (4.9)	8.1-13.3 (3.3-6.9)	8.6 (3.4)	6.5 (3.3)	6.8 (3.6)	4.1 (1.5)	5.8 (1.9)	9.5 (5.8)
Zeeland	4.6 (3.2)	2.7-7.3 (1.7-5.5)	10.2 (5.1)	4.8 (2.8)	6.0 (2.6)	5.4 (2.8)	4.1 (1.6)	14.1 (10.7)
Noord-Brabant	7.1 (3.6)	6.1-8.2 (2.9-4.4)	8.8 (3.3)	7.9 (3.9)	6.9 (3.3)	7.1 (3.6)	6.8 (3.3)	14.5 (8.5)
Limburg	9.2 (4.2)	7.4-11.3 (3.0-5.7)	8.6 (4.1)	5.4 (2.7)	4.2 (2.4)	6.3 (2.7)	5.2 (2.9)	12.0 (6.8)
range for regions (major events)	2.7-10.6 (2.1-5.0)		3.6-11.6 (1.4-5.1)	3.3-9.5 (1.6-5.7)	2.6-7.3 (1.4-3.6)	4.1-7.4 (1.5-5.5)	3.7-8.7 (1.6-4.6)	6.6-16.4 (4.1-10.7)
Netherlands	7.9 (3.5)	7.4-8.3 (3.3-3.8)	9.2 (3.6)	7.2 (3.4)	5.7 (2.5)	6.5 (3.3)	5.7 (2.7)	11.5 (6.6)

[a]   for 2004 until 2006 included coverage data of the corresponding year from Praeventis 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)

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.
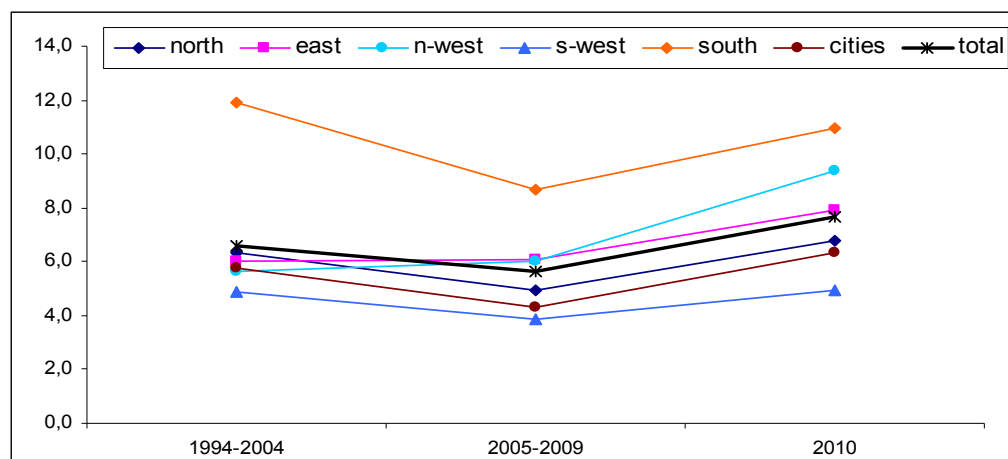

Figure 7   *Reporting rate per 1000 vaccinated infants per region for 2010 compared with*
1994-2004 and 2005-2009

For a break down 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

Proportion	1996-1999	2000-2003	2004	2005-2009	2010
Major AE in all Phone reports	54	54	56	44	46
Major AE in all Written Reports	55	60	65	53	41
1 source for all Minor AE	52	36	18	18	19
1 source for all Major AE	30	15	10	12	10
1 source for all Phone reports	40	24	11	10	10
1 source for all Written reports	44	35	28	24	24
1 source for Major Phone reports	30	14	7	9	8
1 source for Major Written reports	31	30	26	33	22
1 source for All reports	40	25	13	15	15

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). [71]

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.
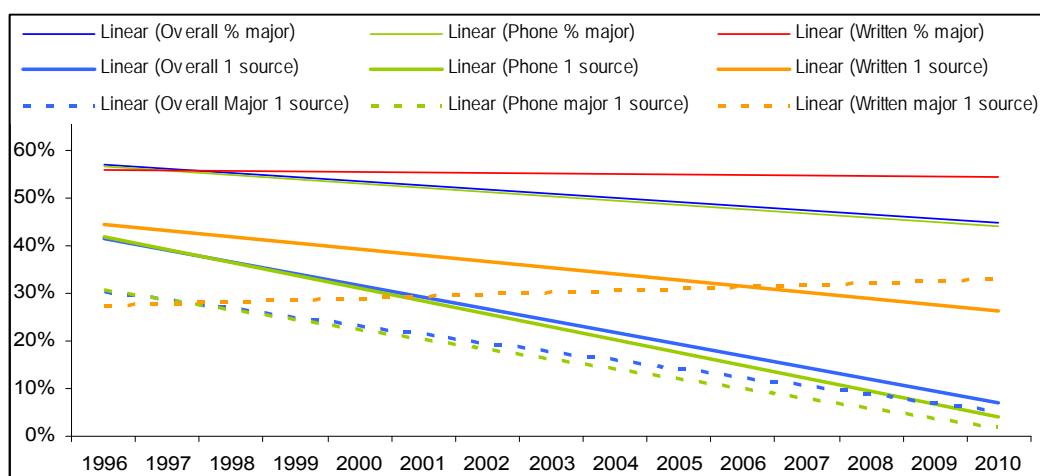
Figure 8   *Trends from 1996-2010 for the proportion of reports with only one information source per type of report.*

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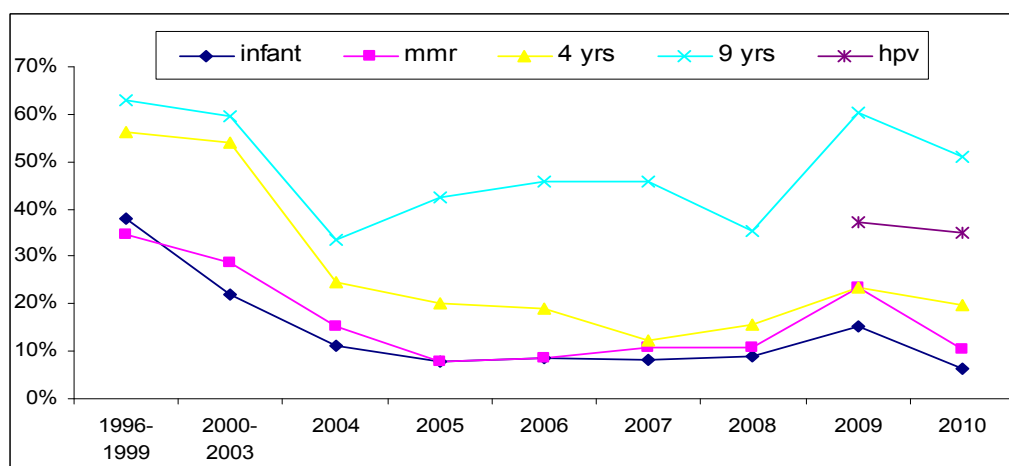
Figure 9   *Proportion single source reports per vaccine dose 1996-2010 (HPV all doses)*

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

vaccine given⇒ scheduled ⇓	dtp-ipv-hib	dtp-ipv-hib + pneu	dtp-ipv-hib-hepb + pneu	mmr	mmr menc	menc	dt-ipv	dtp-ipv	dt-ipv mmr	hpv	other	total 2010	2009	2008	2007	2006	2005
at birth	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
dose 1[j]	5[a]	191	46	-	-	-	-	-	-	-	-	242	287	278	296	285	205
dose 2[j]	4	135	33[b]	-	-	-	-	-	-	-	-	172	186	190	145	195	153
dose 3[j]	4[a]	84[c]	10	-	-	-	-	-	-	-	-	98	128	97	118	99	111
dose 4[j]	6[d]	94[x]	35[e]	-	-	-	1[f]	3[g]	-	-	-	139	148	118	112	154	119
dose?[j]	-	-	-	-	-	-	-	-	-	-	-	0	-	-	1	1	3
mmr0	-	-	-	6[h]	-	-	-	-	-	-	-	6	8	5	4	7	10
mmr1+menC	-	-	-	9[i]	170	3	-	-	-	-	-	182	184	193	174	226	246
dtp-ipv5	-	3	1[j]	-	-	5	1	302[k]	-	-	1[l]	313	604	312	80	98	114
dtp6+mmr2	-	-	-	1	-	1	3[m]	-	77[n]	-	2[o]	84	95	94	62	88	62
menC-camp	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5
hpv	-	-	-	-	-	-	-	-	-	129[p]	-	129	(647)[r]	-	-	-	-
other	-	-	-	-	-	-	-	-	-	-	15[q]	-	7	3	3	6	8
total 2009	19	507	125	16	170	9	5	305	77	129	18	1380	1647[s]	1290	995	1159	1036

[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 + hepB 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 [11]

[s] hpv not included in number of reports of 2009, reported separately in campaign surveillance
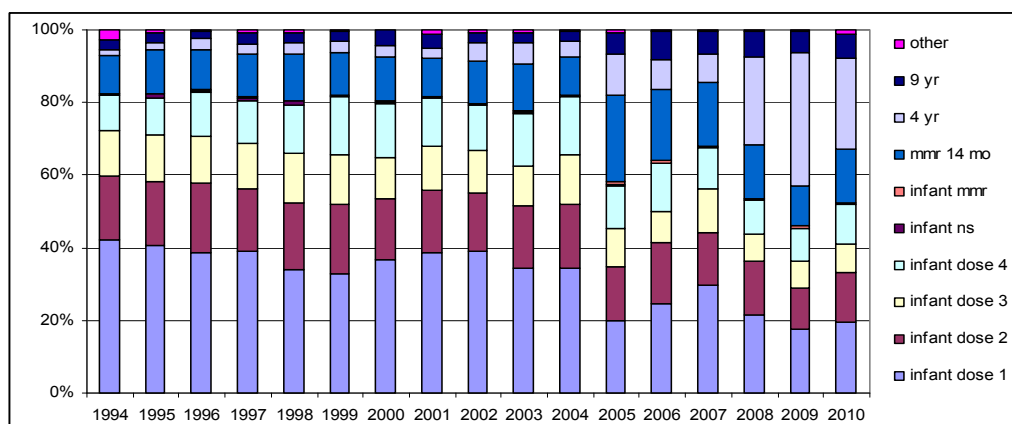
Figure 10   Relative frequencies of vaccine doses in AEFI reports for 1994-2010, without HPV

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 we 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.
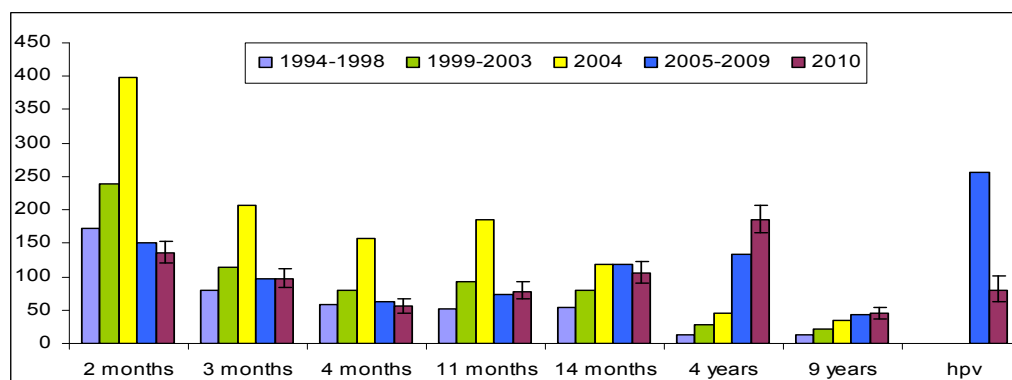
Figure 11A Reporting rate per dose per 100,000 vaccinated children for 1994-2010, with for HPV only first dose included and only 2009 and 2010
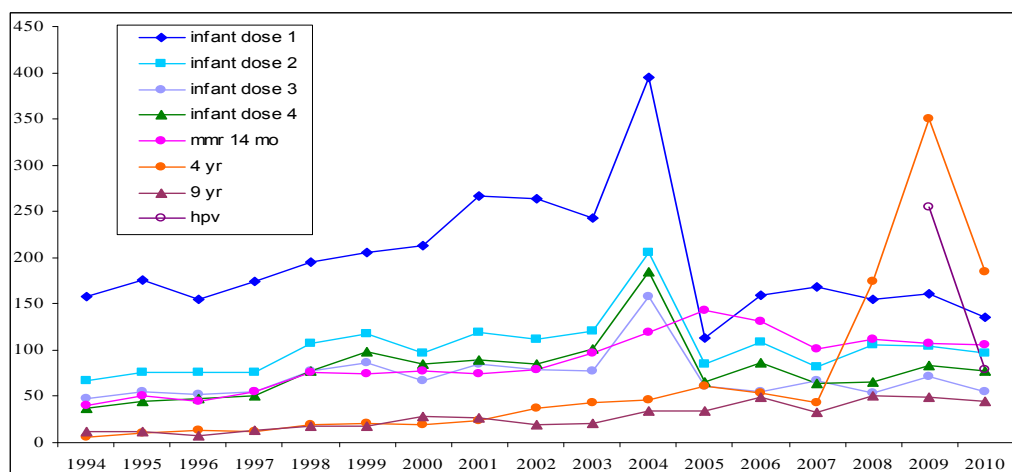
Figure 11B Reporting rate per dose per 100,000 vaccinees for 1994-2010 (HPV dose 1)

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

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

* 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. [14] Remarkable is the lack of reports on the birth dose of HepB vaccine, included since 2003; only once we received such a report (2004).
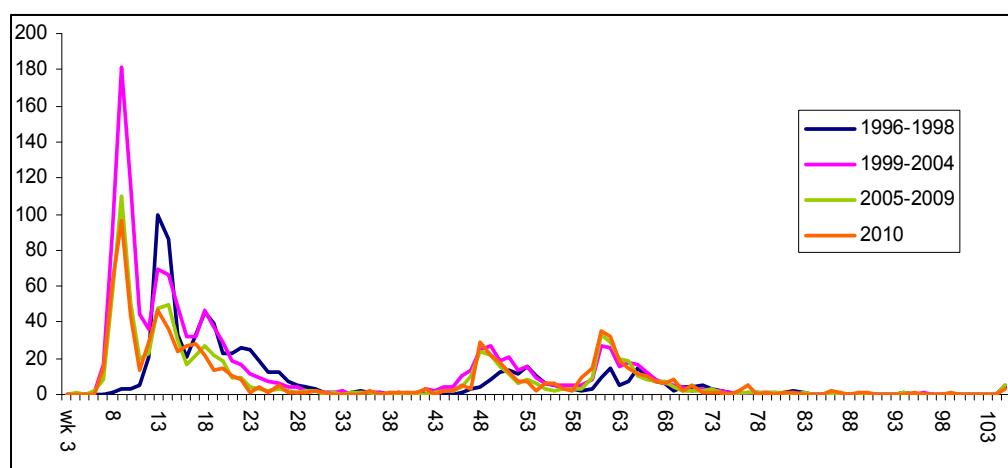
Figure 12   Age distribution of reported children for infant doses and MMR1 for 1996-2010; in 1999 the accelerated schedule was adopted, starting the first dose at 2 months of age

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.
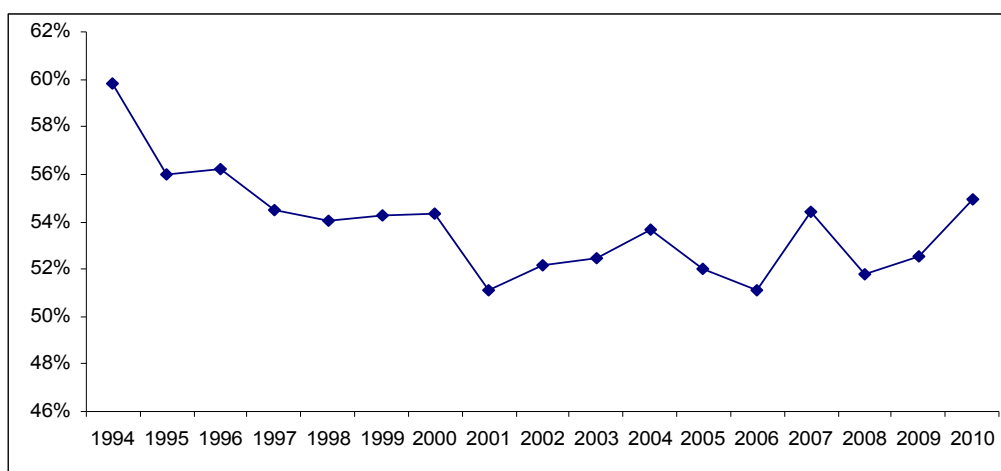
Figure 13   Proportion males in AEFI reports for 1994-2010

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)
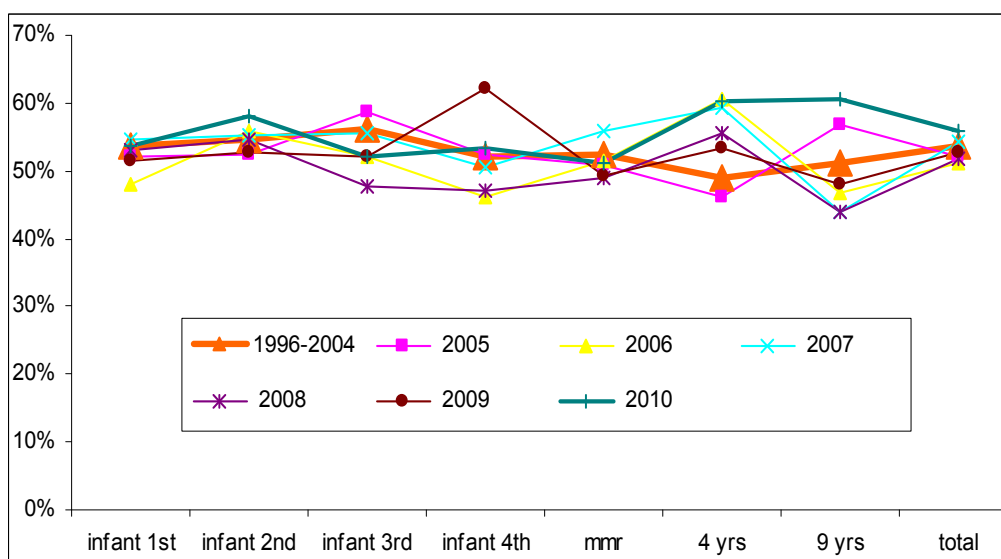
*Figure 14   Proportion males per vaccine dose in 2010 and the 5 previous years,
                compared with the mean for 1996-2004*

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.
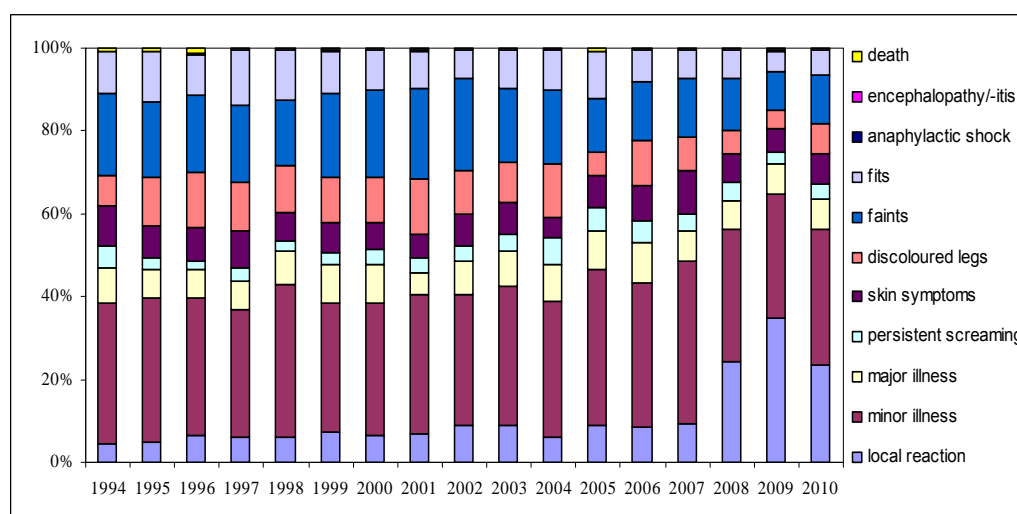
Figure 15   Relative frequencies of event categories of AEFI reports for 1994-2010

The introduction of HPV did not alter the relative distribution of events much because of the rather small number of reports, less than 10% of the total number of reports. See for HPV under section 4.7.2. The bars in Figure 15 depict the relative frequency of reported events in all reports per year. Therefore, an increase in one type of event influences the

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).
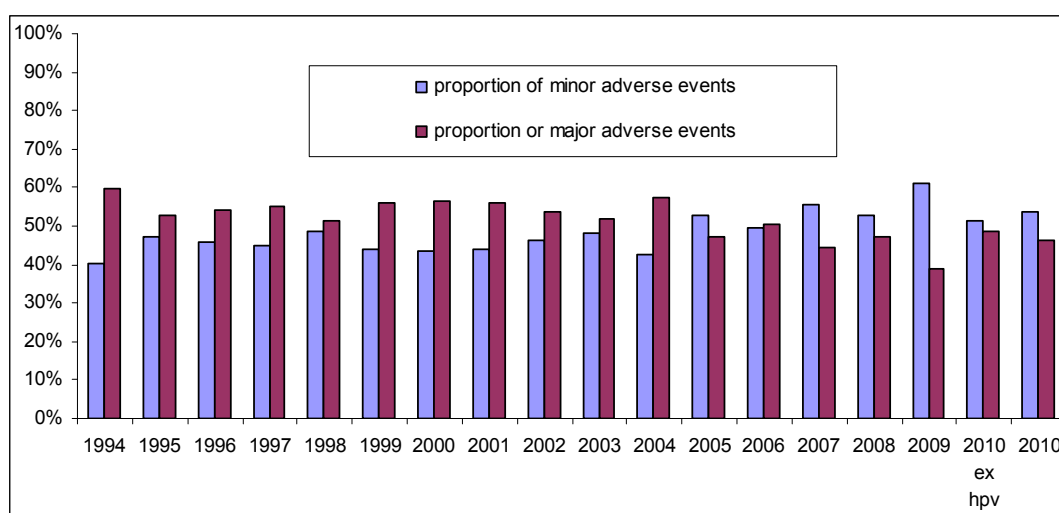
Figure 16A Proportion of reported major and minor AEFI for 1994-2010

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 ($\geq$40.5 °C) cases. The increase in the 9-year-olds reflects increased reporting of fainting. See for specific events under section 4.8.
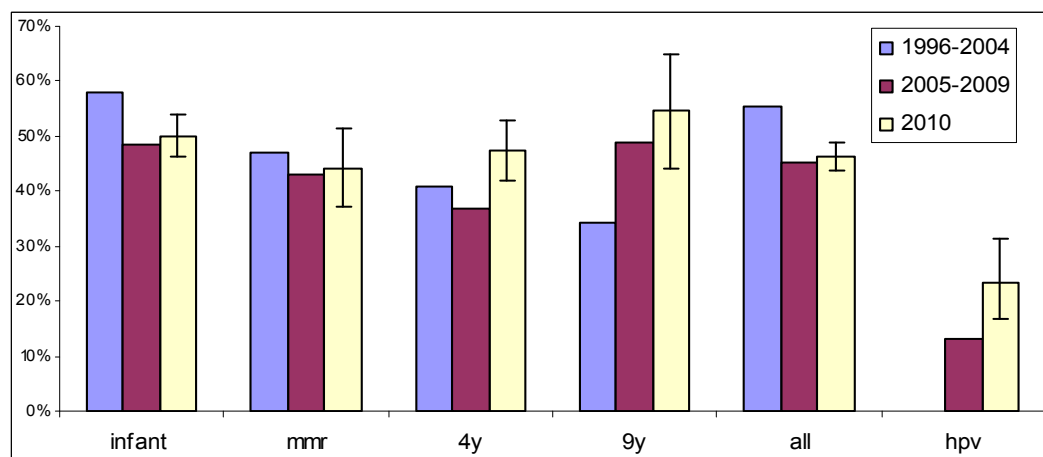
Figure 16B Proportion reported major events per dose for 2010, compared with 1996-2004 and 2005-2009

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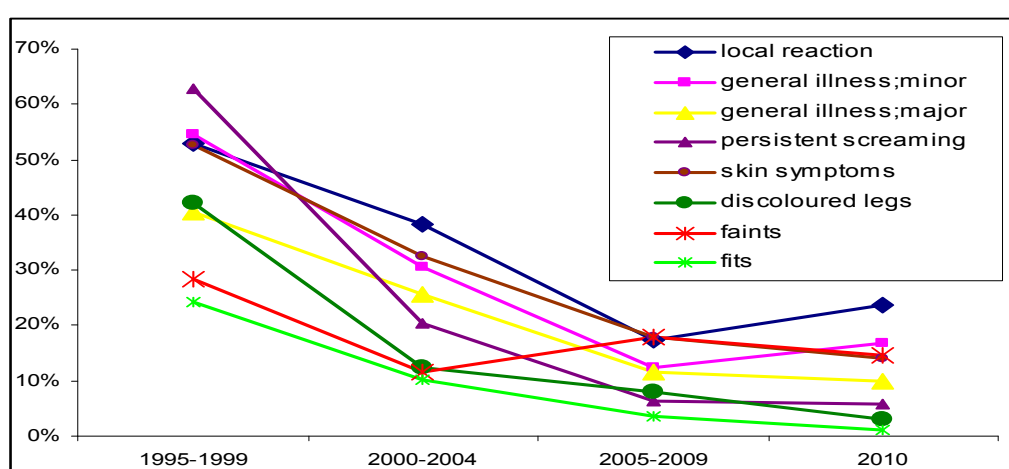
Figure 17   Proportion of reports with single information source and event category for 1995-2010

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

Info																total	%
Info	clinic*	+	+	+	+	+	+	+	+	-	-	-	-	-	-	1200	8
	parent	-	+	+	+	+	-	-	-	+	+	+	+	-	-	1272	9
	GP	-	-	+	-	+	+	+	-	+	+	-	-	+	-	144	1
	hospital	-	-	-	+	+	-	+	+	+	-	+	-	-	-	227	1
event ⇓	other	-	-	-	-	-	-	-	-	-	-	-	-	-	+	1	0
local reaction		38	214	14	6	-	3	-	-	1	7	1	35	2	-	321	
minor general illness		21	296	21	36	5	3	-	-	3	11	2	55	-	1	454	
major general illness		5	46	5	20	6	1	1	3	-	2	6	4	1	-	100	
persistent screaming		1	42	3	5	-	-	-	-	-	-	-	2	-	-	53	
skin symptoms		3	56	6	7	6	2	-	2	1	3	3	-	11	-	100	
discoloured legs		2	74	4	8	-	1	-	-	-	5	3	1	-	-	98	
faints		17	100	3	27	3	-	-	-	-	1	6	7	-	-	164	
fits		1	18	6	44	10	-	-	-	2	-	4	-	-	-	85	
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	
encephalopathy/-itis		-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	
death		-	-	-	2	3	-	-	-	-	-	-	-	-		5	
total 2010		88	846	62	155	33	10	1	5	7	29	25	104	14	1	1380	

[*] 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.
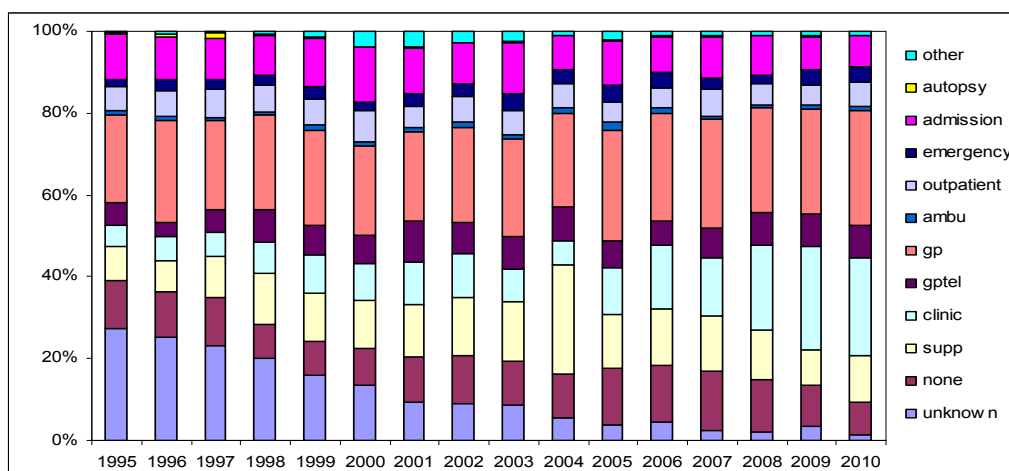
Figure 18A   Relative frequencies of medical intervention level in reports for 1995-2010

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

intervention ⇒ event ⇓	unknown	none	supp[a]	clinic[b]	GPtel[c]	GP[d]	ambu[e]	outpatient	emergency	admission	autopsy	other[f]	2010 total
local reaction	8	24	16	143	27	93	-	6	2	1	-	1	321
minor general illness	6	43	73	79	50	140	-	28	11	15	-	9	454
major general illness	2	1	11	5	10	31	-	11	5	24	-	-	100
persistent screaming	1	8	18	7	3	10	-	-	2	2	-	2	53
skin symptoms	2	3	4	13	10	41	-	17	6	3	-	1	100
discoloured legs	1	12	27	15	2	28	1	4	4	4	-	-	98
faints	-	17	5	67	5	28	5	5	14	18	-	-	164
fits	-	2	1	1	4	15	9	9	8	36	-	-	85
anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-	-	-
encephalopathy/-itis	-	-	-	-	-	-	-	-	-	-	-	-	-
death	-	-	-	-	-	-	-	-	-	2	3	-	5
total 2010	20	110	155	330	111	386	15	80	52	105	3	13	1380

[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 homeopaths

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.
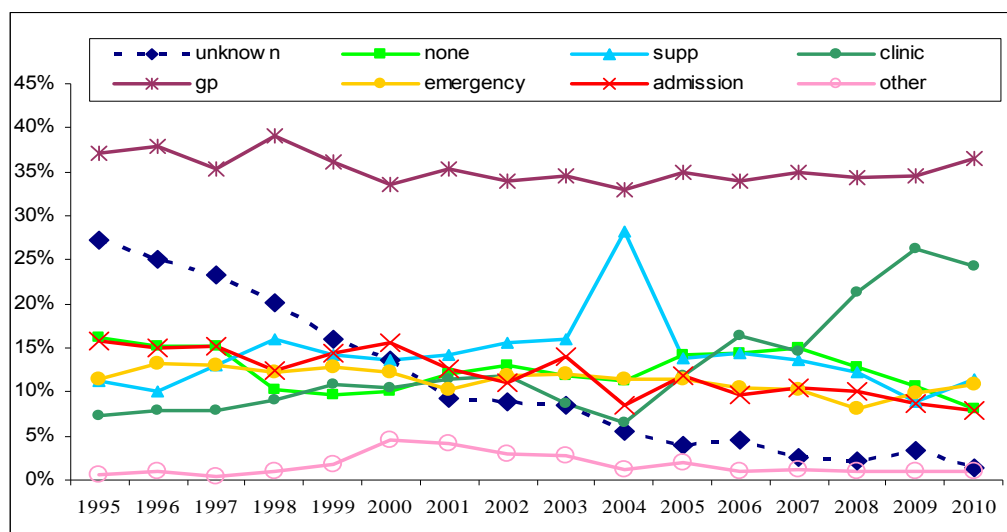
Figure 18B Proportionate distribution of highest level of medical intervention in reported AEFI for 1995-2010

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).
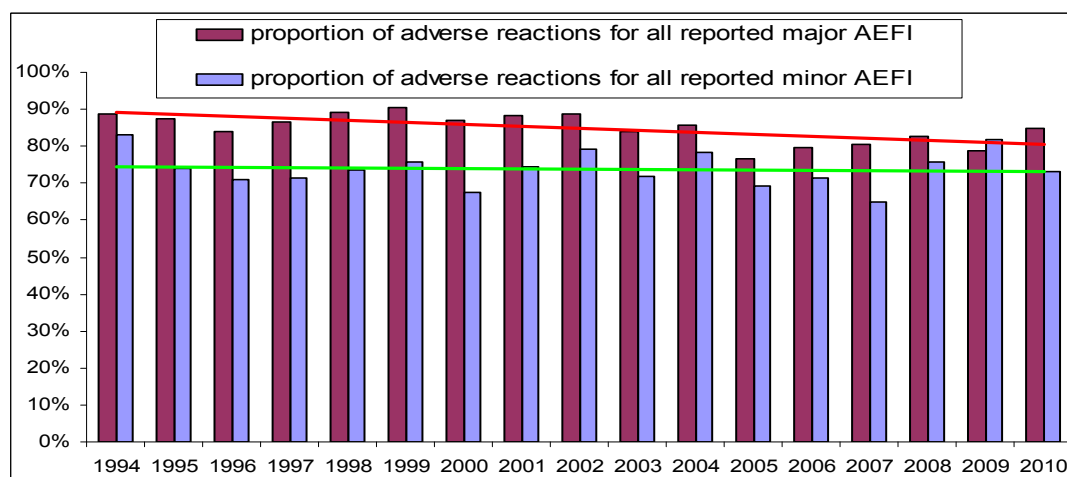
Figure 19   Proportion minor and major AEFI with causality for 1994-2010, with trend lines

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

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

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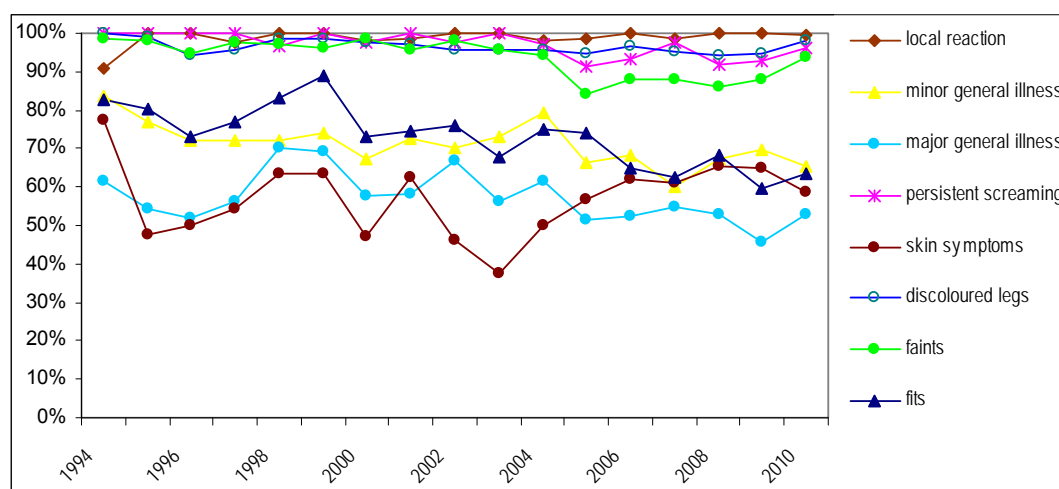
Figure 20   Proportion of assessed causality (AR) in reported AEFI for 1994-2010

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

Proportion causality	1994-2004		2005-2009		2010
	range	mean	range	mean	
local reaction	91-100	98%	98-100	99%	99%
major local reaction	100	100%	100	100%	100%
minor general illness	67-83	74%	60-69	66%	65%
major general illness	52-70	60%	45-55	51%	53%
persistent screaming	97-100	99%	91-98	93%	96%
skin symptoms	38-78	55%	57-66	62%	59%
discoloured legs	94-98	97%	94-97	95%	98%
faints	94-99	97%	84-88	87%	94%
fits	68-89	77%	60-74	66%	64%
total	78-86	82%	72-81	76%	78%

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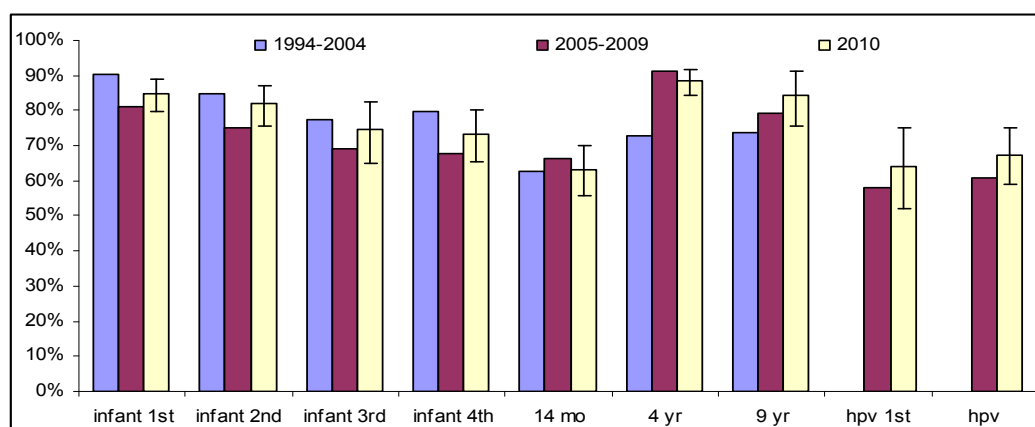
Figure 21   Proportion adverse reactions per scheduled dose for reported AEFI, comparing 1994-2004, 2005-2009 and 2010; for HPV all and 1st doses

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

Proportion causality	1994-2004		2005-2009		2010
	range	mean	range	mean	
Infant 1st dose	86-94	91%	71-86	81%	85%
Infant 2nd dose	78-89	85%	70-81	75%	82%
Infant 3rd dose	69-84	78%	65-74	69%	74%
Infant 4th dose	70-86	80%	63-73	68%	73%
MMR 14 months	49-71	63%	61-70	67%	63%
4 yr booster	60-83	73%	70-96	91%	88%
9 yr booster	55-96	74%	69-87	79%	85%
HPV 1st dose	-	-	58	58%	64%
HPV all doses	-	-	61	61%	67%
Total ex HPV	78-86	82%	72-81	76%	78%

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

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

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.
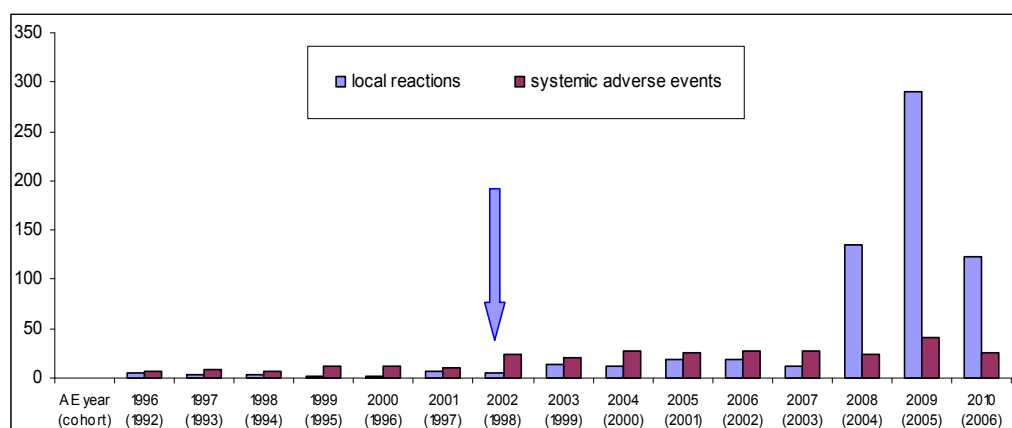

Figure 22   Reported AEFI after booster DT(P)-IPV at 4 years of age, per 100,000 vaccinees for report years 1996-2010 (birth cohorts 1992-2006); arrow depicts start of 4y-booster acellular pertussis

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

cohort	1991-1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Infant **4 doses**	**whole-cell vaccine** **DT-wP-IPV-Hib (+hepB)**								**acellular vaccine** **DTaP-IPV-Hib(+hepB)**	
vaccine	RIVM-DKTP-Hib								Infanrix-IPV-Hib	Pediacel (or InfanrixHexa)
4 **years** **booster**	**No pertussis** **DT-IPV**	**+acellular vaccine** **DT-IPV +aP**					**acellular combined vaccine** **DTaP-IPV**			
vaccine	RIVM-DTP	Single aP added RIVM/GSK					Triaxis -polio	Infanrix-IPV		

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]
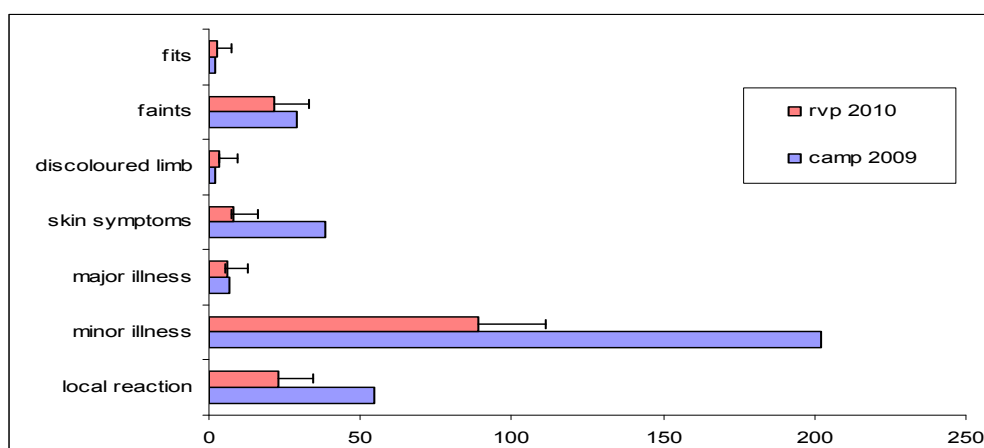

Figure 23A *Reporting rate per 100,000 vaccinees for different event categories, HPV 2009 campaign compared with 2010 RVP (with some catch-up campaign girls)*
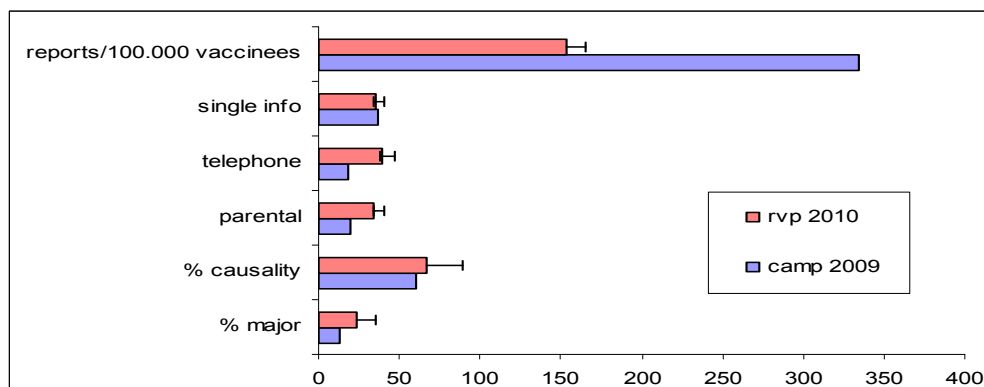
Figure 23B *Reporting rate per 100,000 vaccinees, for all HPV doses, for reports by telephone, parental and single information reports and overall proportion of major reports and proportion with causal relation, HPV 2009 campaign versus 2010 RVP (with some catch-up campaign vaccinations)*

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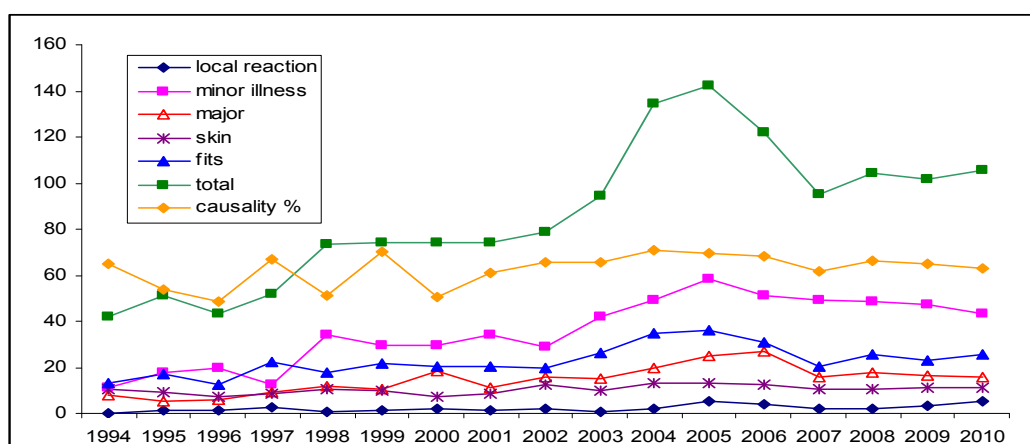
Figure 24A Reporting rate for MMR1 per 100,000 vaccinees and type of events with overall proportion with assessed causality for 1994-2010.

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).
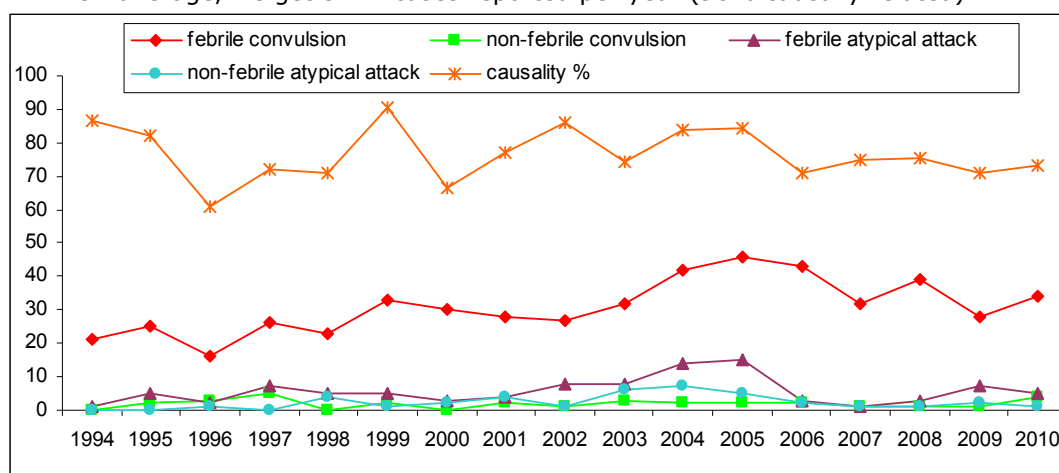

Figure 24B Number of reports per type of fit after MMR1 and proportion of assessed causality for 1994-2010

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.
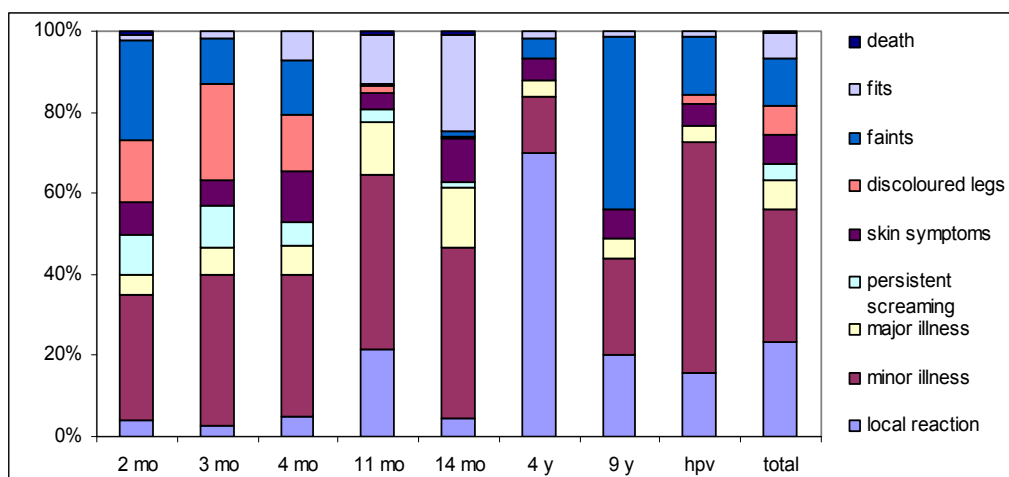

Figure 25   Relative frequencies of event categories per dose for reported AEFI in 2010
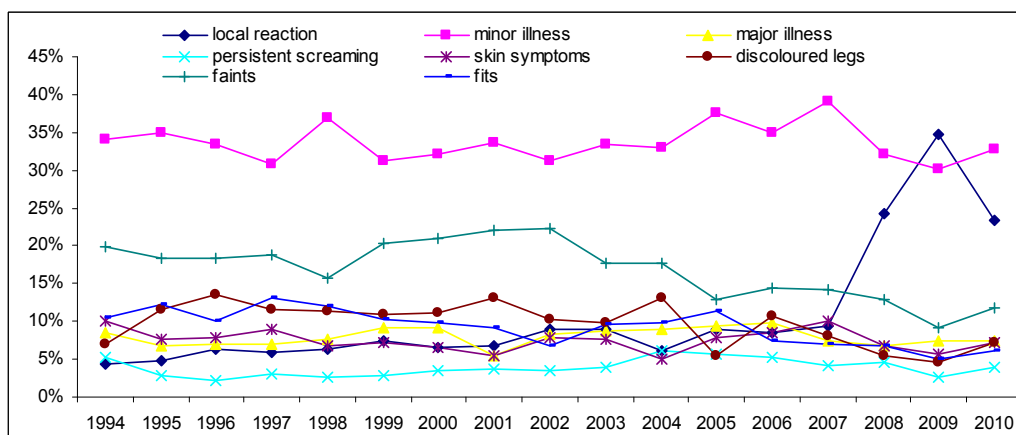

Figure 26A Proportion of reports in the different event categories for 1994-2010
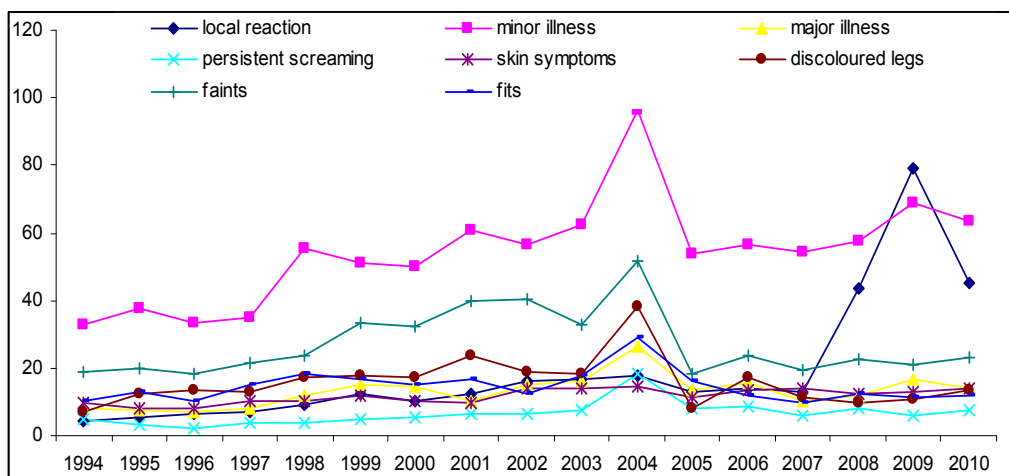

Figure 26B Reporting rate per event category per 100,000 vaccine doses for 1994-2010

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.

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

| event ⇓ sex ⇒	2010 total*	m%*	2009 total	m%	2008 total	m%	2007 total	m%	2006 total	m%	2005 total	m%
local reaction	302	59	571	54	313	54	93	51	102	46	93	48
general illness minor	379	58	498	52	414	56	390	52	403	55	389	56
general illness major	95	57	121	49	87	62	73	47	111	52	97	53
persistent screaming	53	58	42	53	60	55	42	54	61	47	58	50
skin symptoms	93	56	95	57	88	55	101	54	97	49	82	53
discoloured legs	95	52	76	43	70	51	81	50	124	51	57	53
faints	146	52	150	53	165	53	141	50	169	51	75	54
fits	83	42	83	47	88	48	69	47	85	53	71	56
anaphylactic shock	0	-	-	100	1	-	-	-	-	-	-	-
encephalopathy/-itis	0	0	2	0	1	0	1	100	1	100	1	0
death	5	60	9	0	3	75	4	83	6	38	8	25
total	1251	56	1647	52	1290	54	995	51	1159	52	1036	54

* ex hpv
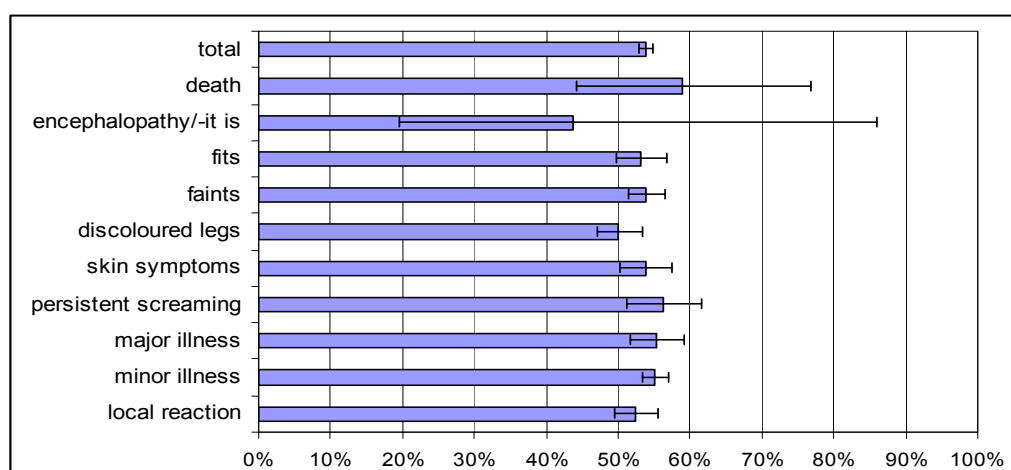
Figure 27   Male proportion in reported AEFI for 1994-2010

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

event	2010 (major)	AR	2009 (major)	2008 (major)	2007 (major)	2006 (major)	2005 (major)	2004 (major)
inflammation	268 (130)	268	535 (150)	286 (125)	65 (25)	78 (20)	55 (7)	60 (10)
abscess/ cellulitis	3 (3)	3	7 (7)	6 (6)	5 (5)	6 (6)	13 (13)	14 (14)
pustule/erysipelas	1 (1)	1	-	-	-	-	1 (0)	1 (0)
atypical reaction	33 (2)	32	15 (0)	10 (0)	11 (0)	14 (2)	18 (0)	29 (0)
haematoma	4 (0)	4	-	3 (0)	1 (0)	-	-	2 (0)
nodule	10 (0)	10	10 (0)	7 (0)	5 (0)	1 (0)	4 (0)	6 (0)
avoidance	2 (0)	2	4 (0)	1 (0)	3 (0)	3 (0)	2 (0)	17 (1)
total (major)	321 (136)	320	571 (157)	313 (131)	93 (30)	102 (28)	93 (20)	129 (25)

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.
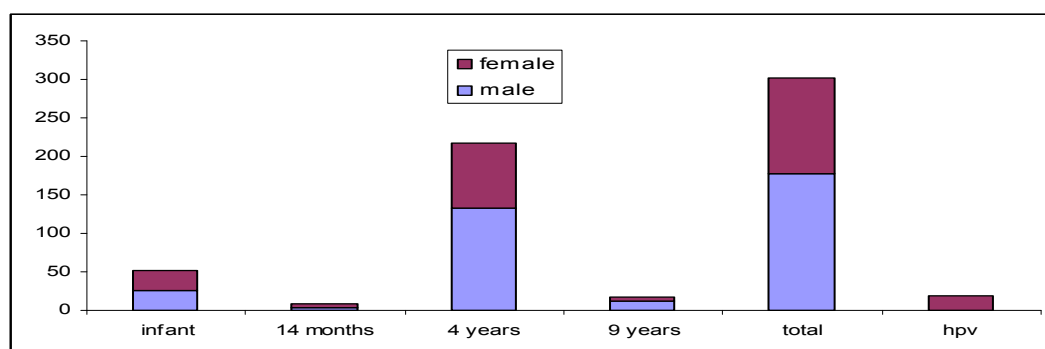
Figure 28   Proportion males in reported local reactions for 2010

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).
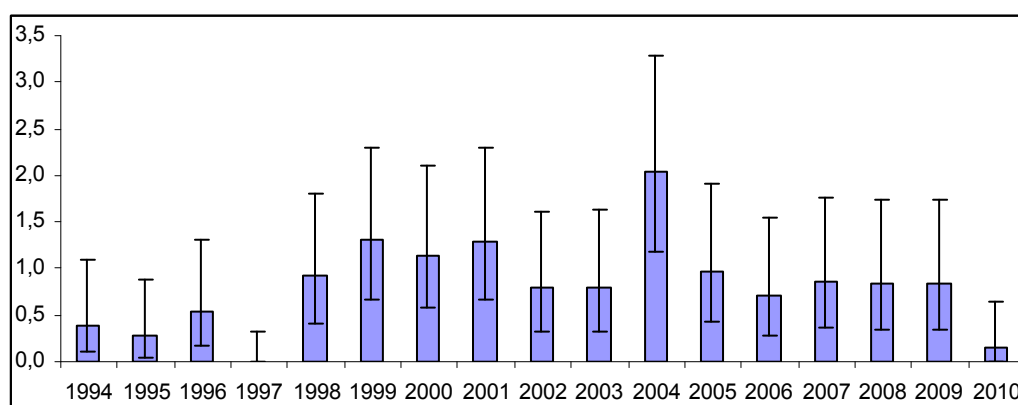

Figure 29   Reporting rate of reported abscesses after infant vaccinations per 100,000 doses for 1994-2010

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

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

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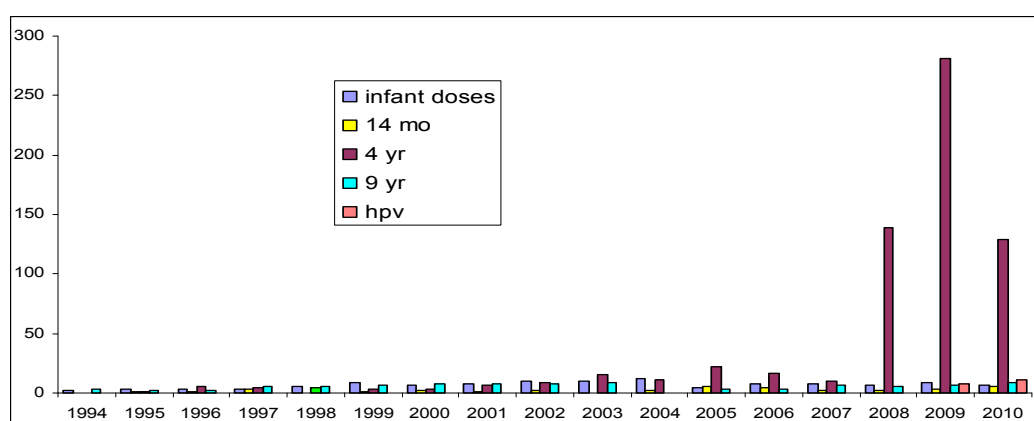
Figure 30   *Local reactions per vaccine dose with reporting rate per 100,000 vaccinees for 1994-2010, for HPV only reports after first dose were included*

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.
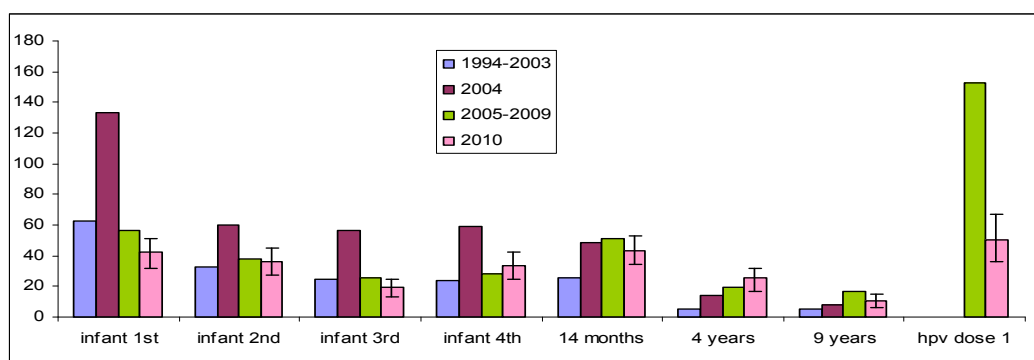
Figure 31   Reporting rate for minor general illness per 100,000 vaccinees for 1994-2010; for HPV only reports after the first dose are included

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)

Symptom or diagnosis	2010	AR[*]	2009	2008	2007	2006	2005	2004
fever	214	177	258	159	128	135	120	212
crying	36	30	33	64	56	61	57	157
pallor and/or cyanosis	11	10	10	19	11	16	20	83
myoclonics and chills	17	14	15	5	14	9	7	46
prolonged/deep sleep/sleeping	12	12	10	14	10	14	7	10
rash(illness)	31	2	26	37	33	52	38	34
vaccinitis	20	20	37	33	23	24	39	31
respiratory tract disorders	21	3	25	18	36	21	22	28
gastro-intestinal tract disorders	36	9	36	30	31	39	17	28
arthralgia/arthritis/coxitis/limping/ imbalance/pain in limbs	16	7	6	5	3	5	18	6
behavioural problems/-illness	9	3	10	8	7	5	1	12
headache, dizziness, fatigue, lethargy	16	9						
other&	15	0	32	22	38	22	43	57
total	454	296	498	414	390	403	389	704
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.
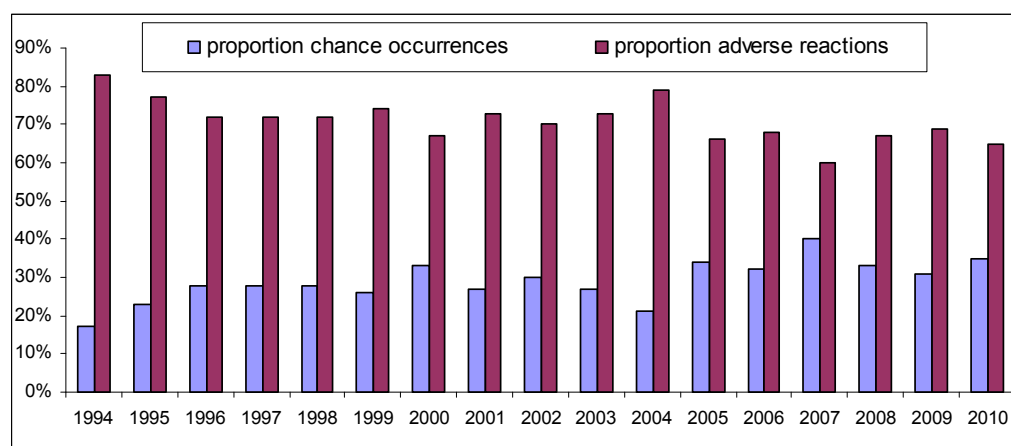

Figure 32 Proportion of adverse reactions and coincidental events in minor general illness reports for 1994-2010

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%

(mean 26%). The proportion of adverse reactions decreased a little since the introduction of acellular DTP-IPV-Hib in 2005 (Tables 11 and 12, Figure 32).
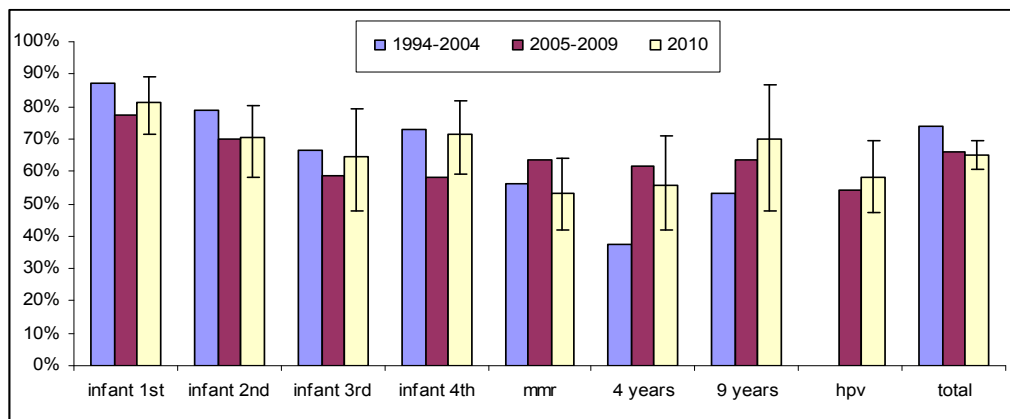

Figure 33   Proportion Adverse Reactions in minor general illness category per dose for 2010, compared with the mean over 2005-2009 and 1994-2004

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.
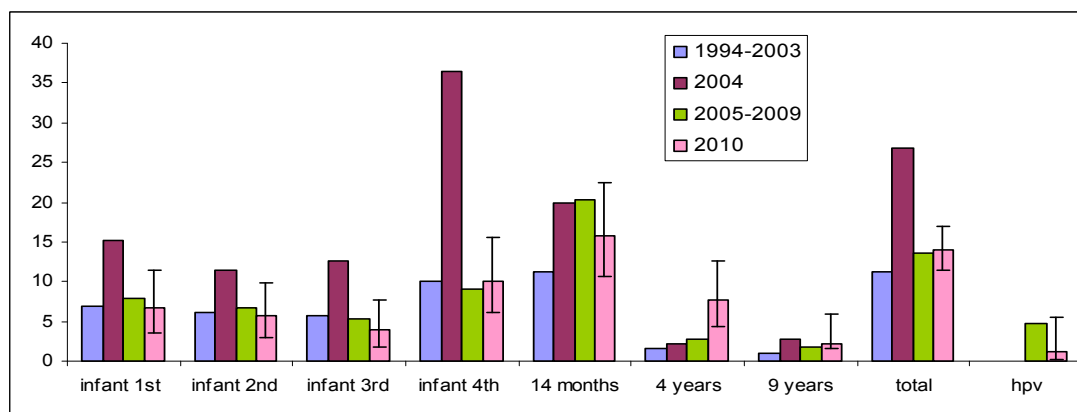
Figure 34   Reporting rate per dose for major illness in 2010, compared with previous years; for HPV only first doses are included and totals are without HPV

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 ($\geq$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)*

symptom or diagnosis	2010	AR[*]	2009	2008	2007	2006	2005	2004
very high fever (≥ 40.5 °C)/extreme hypothermia	51	38	53	36	41	53	37	123
chills/myoclonics, accompanied with very high fever	0	-	1	-	-	2	1	5
gastro-intestinal tract disorder	1	0	4	3	1	4	2	7
respiratory tract disorder, apnoea, respiratory insufficiency	6	2	13	8	6	11	7	6
meningitis	1	0	3	3	7	4	5	3
vaccinitis/rash illness, accompanied with very high fever	9	6	6	15	2	17	13	6
Infectious disease ns	3	0	10	3	2	2	-	-
arthritis/osteomyelitis/JIA/myopathy	4	2	6	5	2	1	4	4
cardiomyopathy/myocarditis/arrhythmia/vasculitis	0	-	3	-	1	2	1	1
ITP	7	4	1	2	4	1	7	15
cerebellar ataxia	1	0	-	-	-	1	-	-
endocrinological disorder/metabolic disease	1	0	4	-	-	1	1	2
kawasaki	0	-	1	-	1	-	2	2
neurological disorders	0	-	5	-	-	-	-	2
optic neuritis/atrophy/visual disorder	1	0	-	-	-	1	-	-
intussusception	0	-	-	-	-	-	-	2
facial paralysis	1	0	-	-	-	-	2	-
urogenital tract disorder/henoch schonlein	3	0	1	1	1	-	1	5
retardation/autism/pervasive-behavioral disorder	3	0	4	3	3	2	7	5
lymphadenitis colli/abcess/cellulitis	0	-	-	1	-	3	1	-
ALTE	1	0	2	2	-	-	-	2
shaken baby syndrome	1	0	-	-	-	-	-	1
other	6	1	4	5	2	6	3	2
total	100	53	121	87	73	111	97	194

* 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+Pneu 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 erythroblastaemia 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.
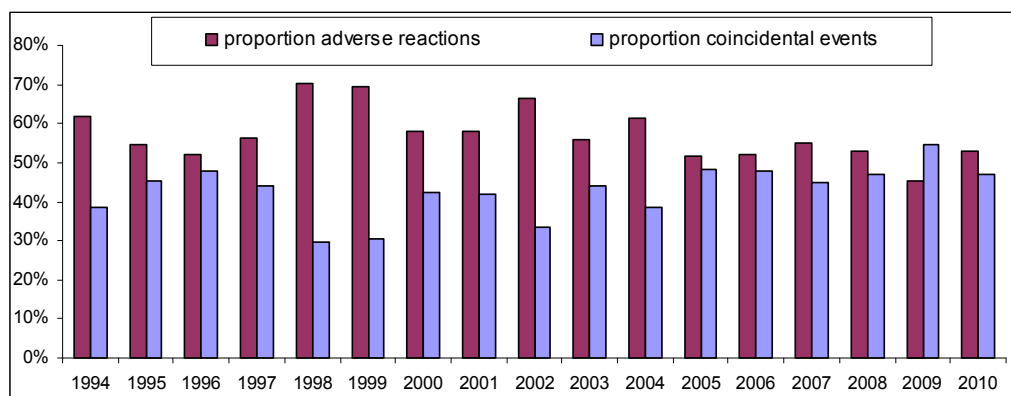

Figure 35   Proportion of adverse reaction in reported major general illness for 1994-2010
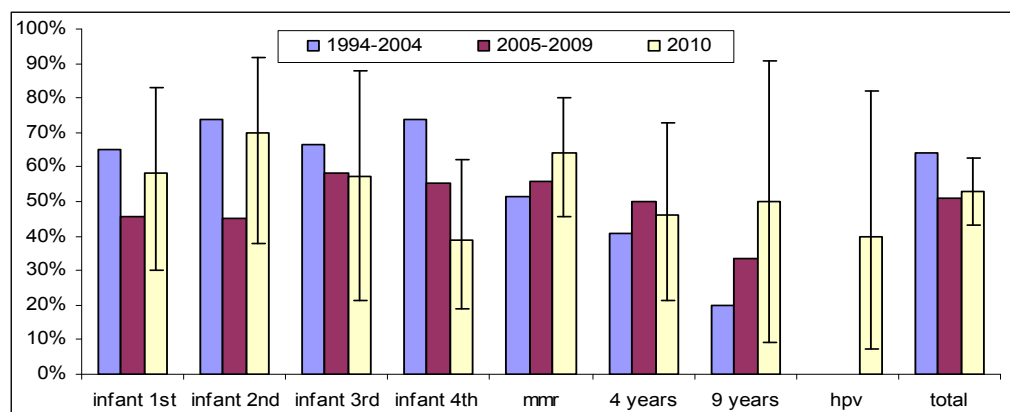
*Figure 36   Proportion Adverse Reactions in major illness category per dose for 2010,
compared with the mean over 2005-2009 and 1994-2004*

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
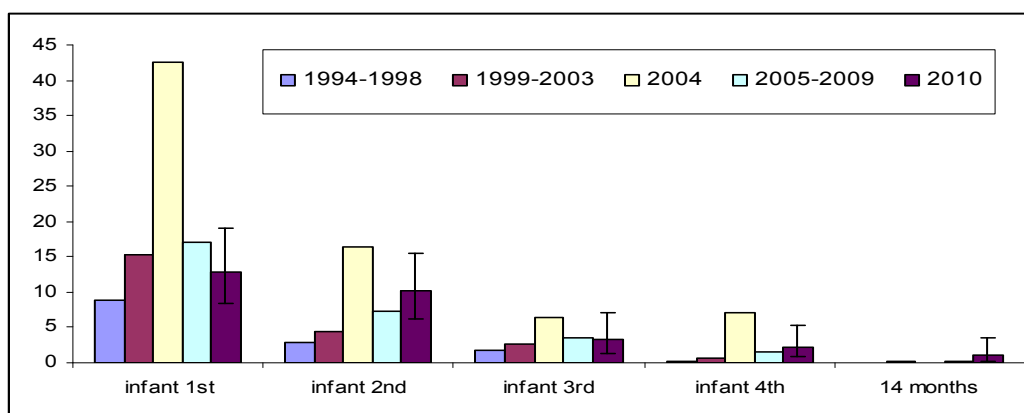syndrome.

Figure 37   Reporting rate per dose for persistent screaming for 1994-2010

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)

diagnosis	2010	AR[*]	2009	2008	2007	2006	2005	2004
angio-oedema/swelling	9	4	6	9	11	5	10	10
exanthaema/erythaema	51	27	46	48	55	52	46	60
urticaria	13	6	10	16	9	18	7	8
eczema (increase)	18	16	23	7	13	16	16	13
petechiae/purpura	5	5	2	1	4	3	2	5
other	4	0	8	7	9	3	1	10
total	100	58	95	88	101	97	82	106

* 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.
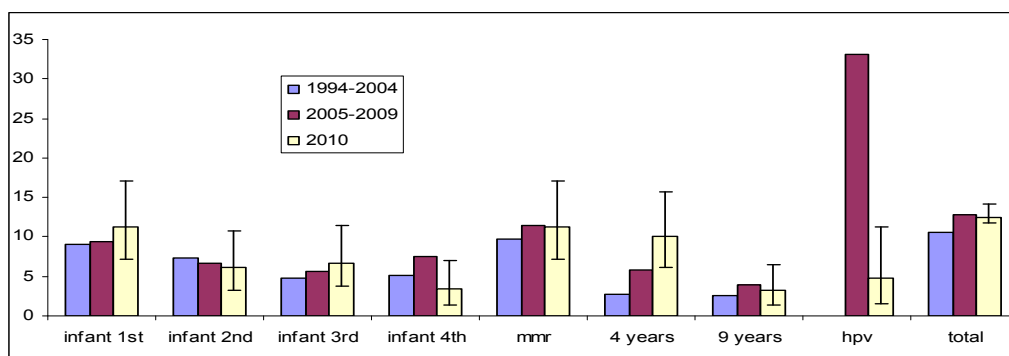
Figure 38   Reporting rate for general skin symptoms, per dose per 100,000 vaccinees in 2010, compared with 2005-2009 and 1994-2004 (HPV first dose only)

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.
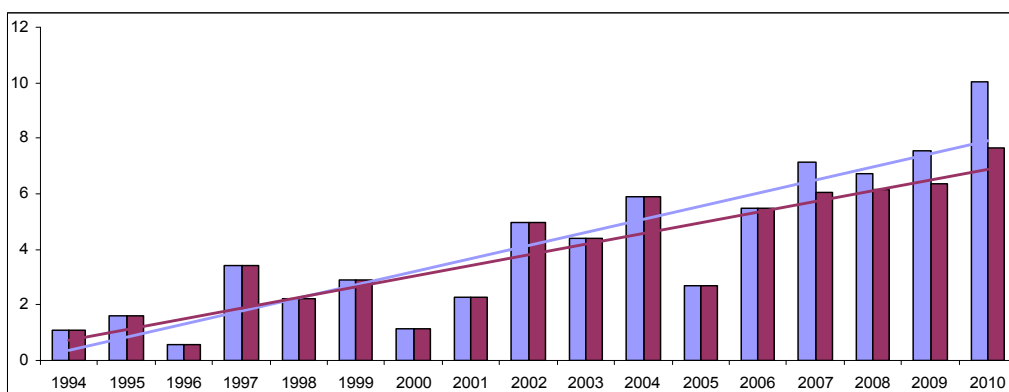
Figure 39   Reported skin symptoms after 4y-boosters; rate per 100,000 vaccinees for 1994-2010 (blue bars), compared with rates for recent vaccinations only (burgundy red bars)

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.

Figure 40A Reporting rates the most frequently reported skin symptoms per 100,000 vaccinees for 2010, compared with 1994-2004 and 2005-2009
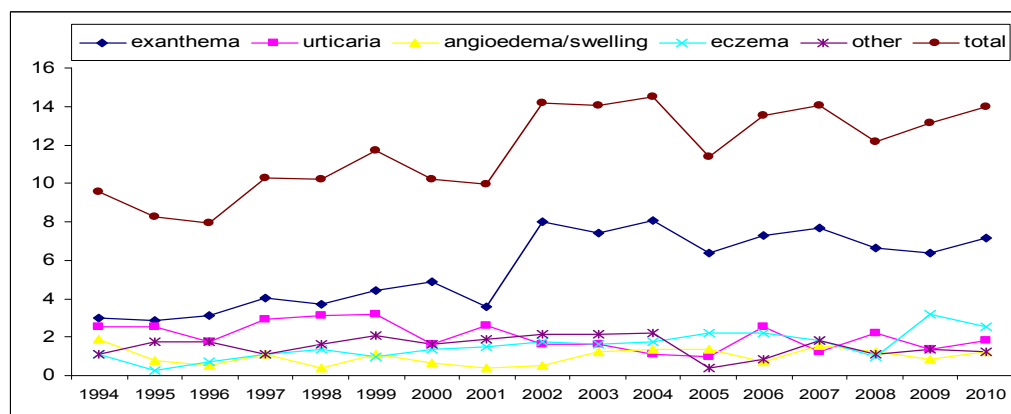
Figure 40B Reporting rate per 100,000 vaccinees for the most common skin symptoms for AEFI in 1994-2010

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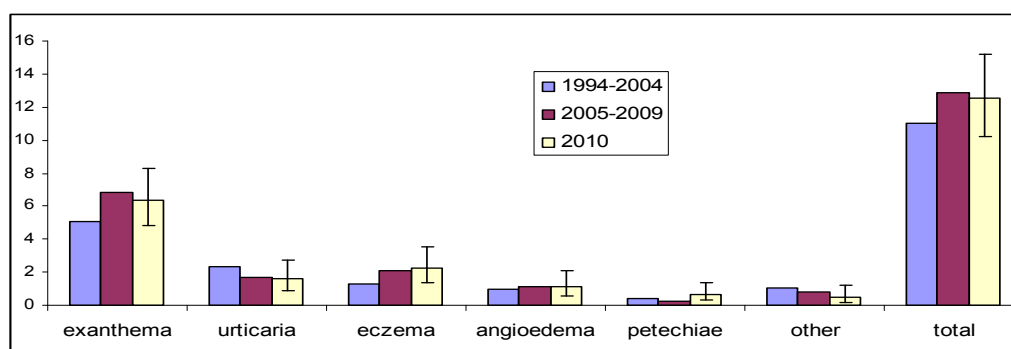 with simultaneous MenC, the proportion causality was 60% for both 2010 and 1994-2009 (range 35-82%). For HPV the reporting rate was high in 2009 and low in 2010 (all doses) but the proportion causality was similar with 30% and 29% respectively. For the other doses fluctuation is very large because of 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%.
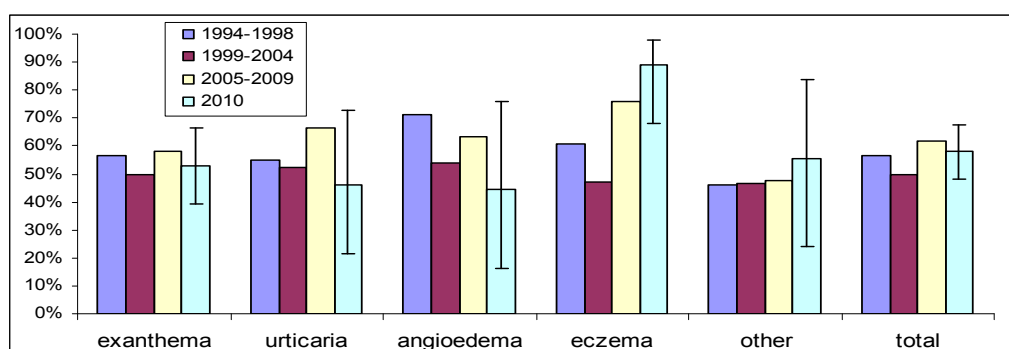
Figure 41   Proportion causality for the most reported skin symptoms for 1994-2010

4.8.6   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

diagnosis	2010	AR*	2009	2008	2007	2006	2005	2004
blue legs	16	16	10	6	6	12	5	36
red legs	41	41	38	35	49	60	26	130
purple legs	27	27	17	15	12	30	8	69
petechiae only	12	11	9	14	11	19	15	40
swollen limb	2	1	2	-	1	3	3	4
total	98	96	76	70	79	124	57	279

* number of adverse reactions

Figure 42   Reporting rate of discoloured legs per dose per 100,000 vaccinees in 2010, compared with 1994-1998, 1999-2003, 2004 and 2005-2009
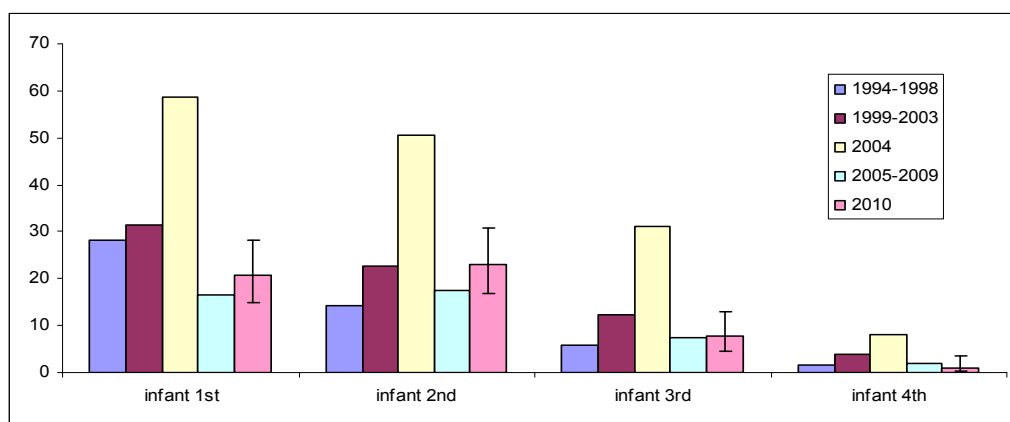
Since 2005, there have been many changes in the schedule and in the type of included vaccines. The influence on the (rate of) occurrence of discoloured legs and on the distribution over the different doses needs more in depth analysis, requiring detailed denominators from the vaccination register.
Causal 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.
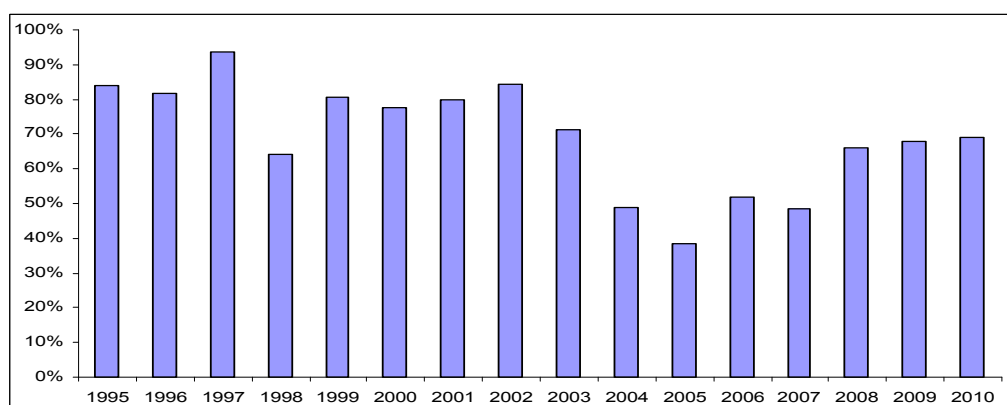

Figure 43   Proportion of double-sided discoloured legs for 1995-2010

4.8.7   Faints

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

diagnosis	2010	AR*	2009	2008	2007	2006	2005	2004
collapse	91	90	89	95	96	76	75	318
breath holding spell	4	4	18	9	14	11	6	23
fainting	69	68	43	61	31	82	52	37
total	164	162	150	165	141	169	133	378

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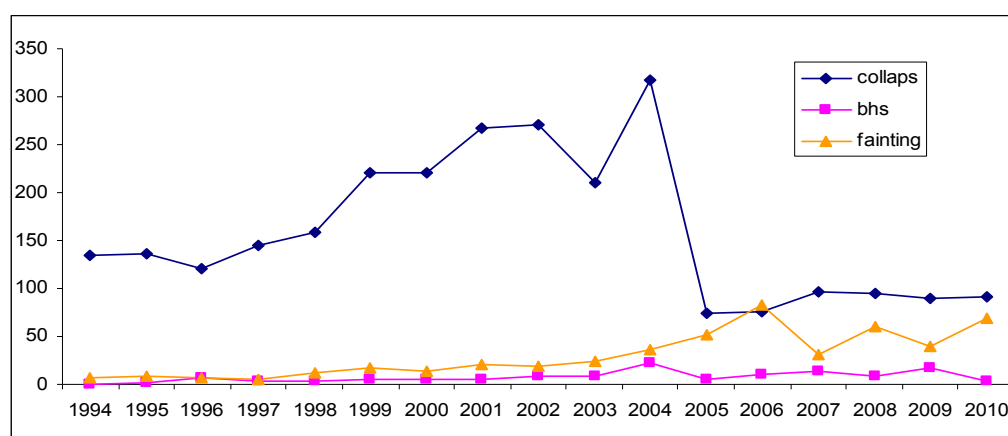
Figure 44   Absolute numbers of reported faints for AEFI per type of event in 1994-2010

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.
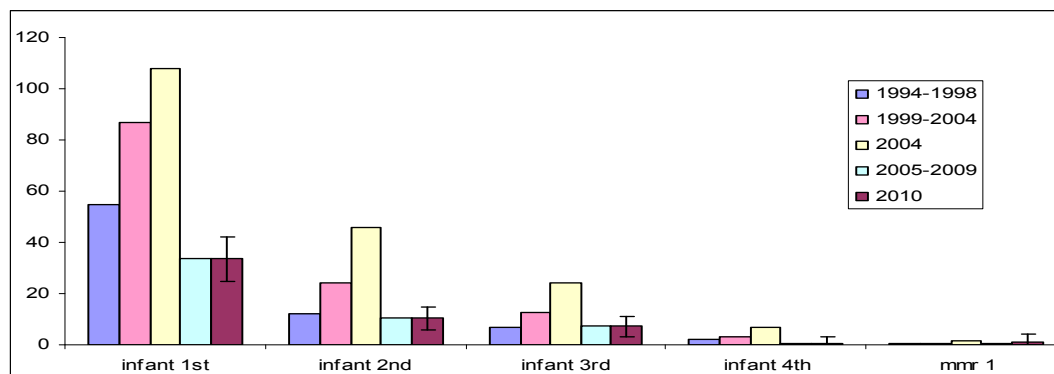
Figure 45   Reporting rate per dose for collapse and BHS per 100,000 vaccinees in 2010, compared with the means for 1994-1998, 1999-2003, 2004 and 2005-2009.
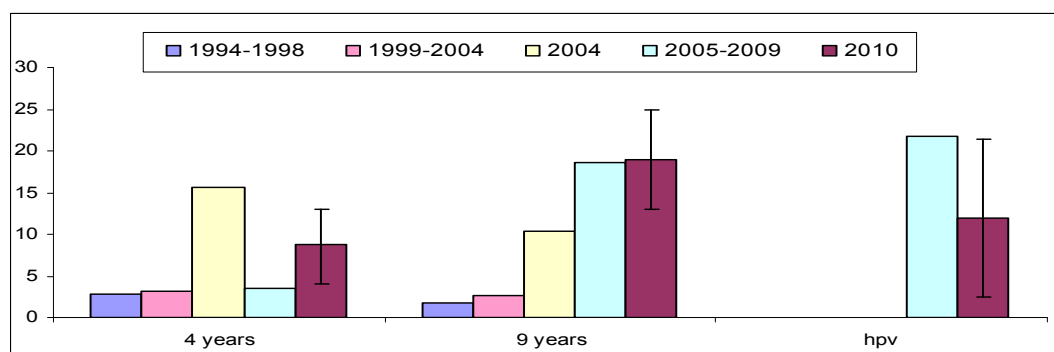
Figure 46   Reporting rate of faints after 4y- and 9y-boosters and the first dose of HPV in 2010, compared with the means for previous periods

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 47   Proportion of reports with causal relation with the vaccinations for AEFI in the faints category for 1994-2010

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

diagnosis		2010	AR*	2009	2008	2007	2006	2005	2004
febrile convulsion	simplex	21	14	18	23	25	30	34	45
	complex	18	12	17	27	13	24	24	32
	atypical	10	9	4	6	4	3	7	13
non febrile convulsion		8	6	6	4	3	6	6	8
epilepsy		4	0	6	4	6	3	4	9
atypical attack		24	13	32	24	18	19	43	104
total		85	54	83	88	69	85	118	211

*   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).
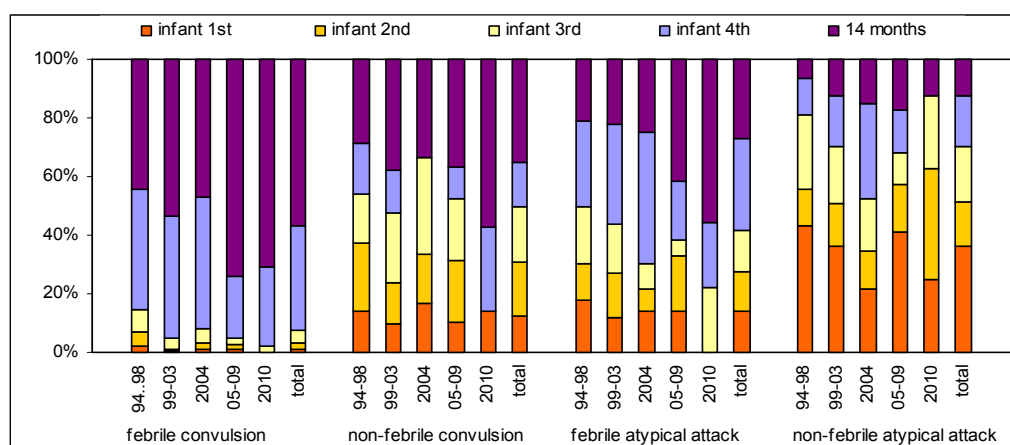
Figure 48A Proportion febrile and non-febrile events in the fits event category for 2010, compared with 1994-1998, 1999-2003, 2004 and 2005-2009
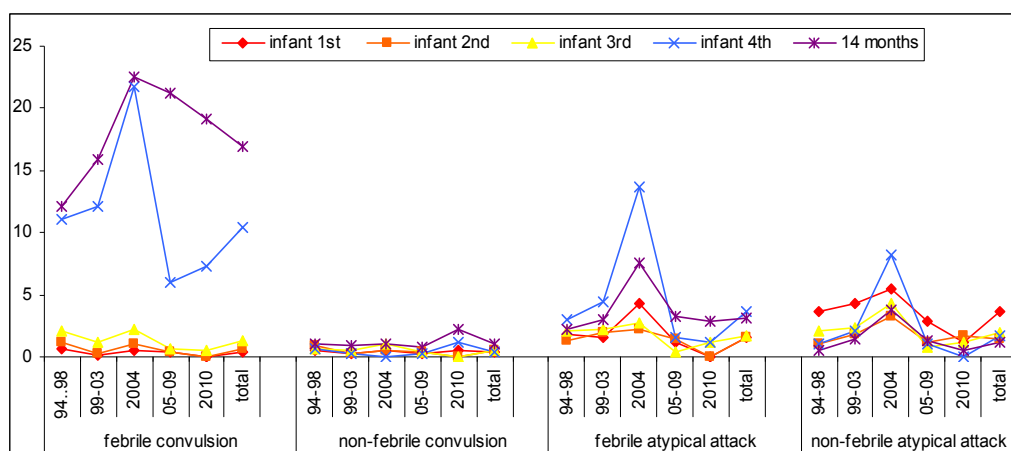
Figure 48B Reporting rates per 100,000 vaccinees per dose for febrile and non-febrile fits in 2010, compared with 1994-1998, 1999-2003, 2004 and 2005-2009
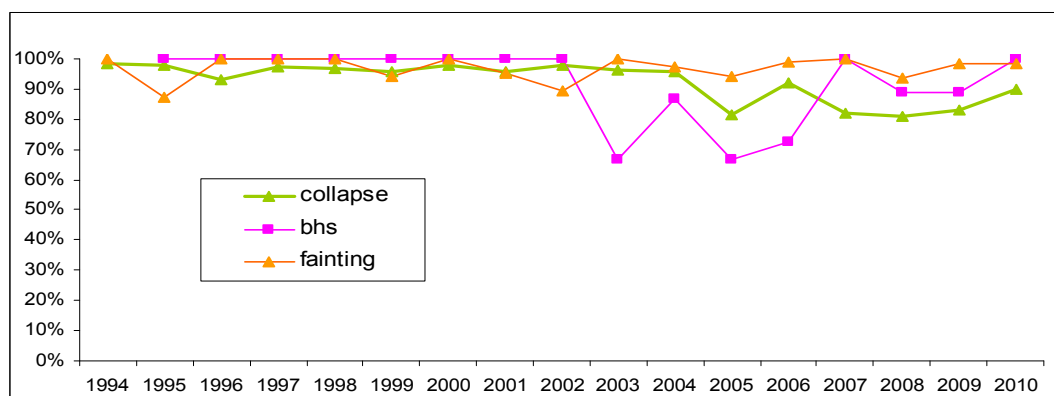
The distribution of reports in this event category over the different doses is illustrated in Figure 49, with rates per 100,000 vaccinees for all types of reported fits together. The summarised period 1999-2004 comprises 2004 with a very high rate for reported fits, apparent for all infant doses, but 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).
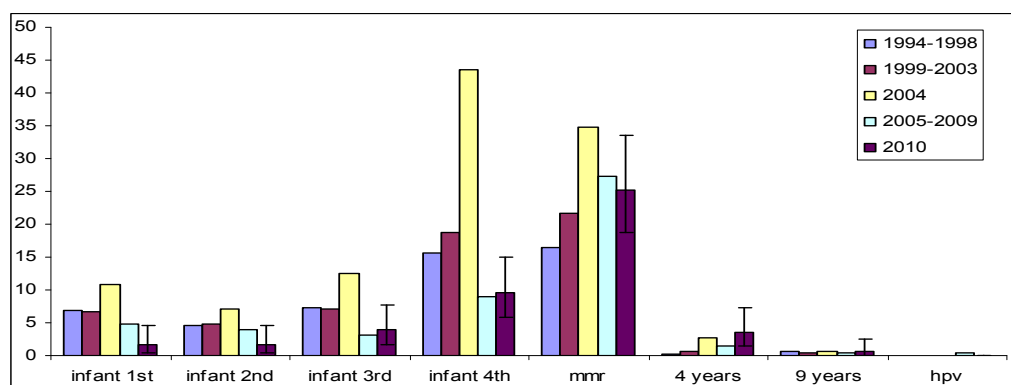
Figure 49   Reporting rate per dose per 100,000 vaccinees for fits in 2010, compared with 1994-1998, 1999-2003, 2004 and 2005-2009

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.
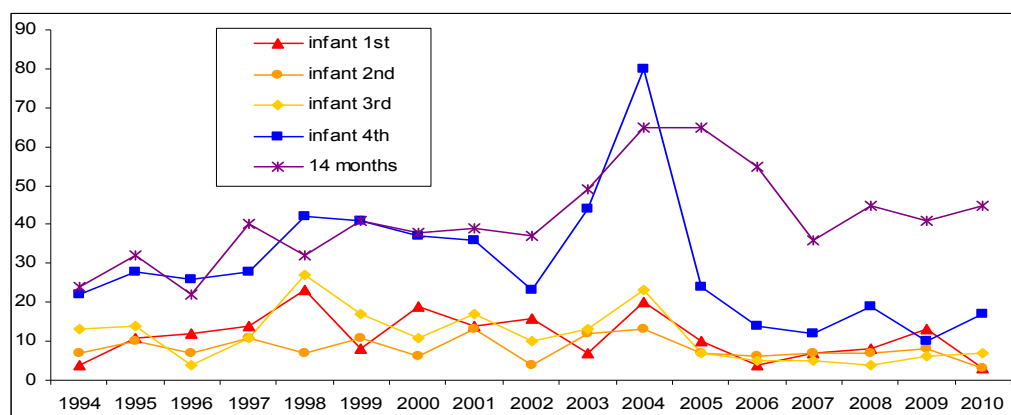
Figure 50   Reporting rate per 100,000 vaccinees for fits after infant doses and MMR, 1994-2010

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.
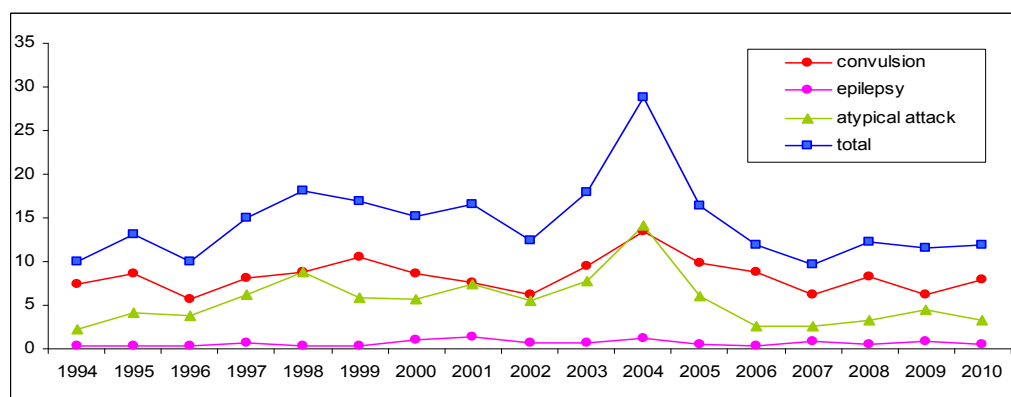
Figure 51   Reporting rates for fits per type of event per 100,000 vaccinees in 1994-2010

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.
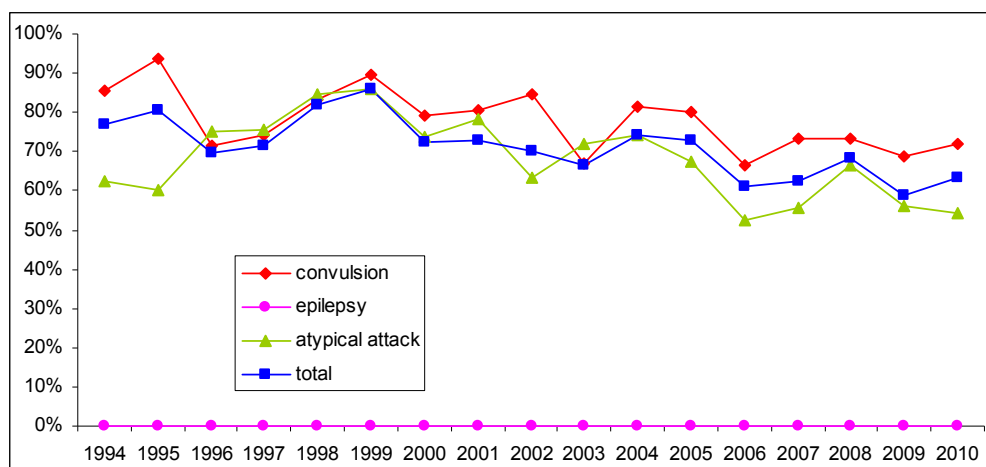
Figure 52   Proportion reports with causality per (working) diagnosis for 1994-2010

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 inversed 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

child	sex	age[a]	vaccines	time interval		symptoms/diagnosis	caus ality	auto psy
				illness	death			
A	m	11 m	dtp-ipv-hib + pneu 4	1m	1.1m	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.	no	no
B	f	15 m	mmr1 + menC	11d	12d	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.	no	yes
C	m	8 w	dtp-ipv-hib-hepb + pneu 1	5 d	8 d	Convulsions, vomiting and diarrhoea, dehydration and extensive cerebral oedema with loss of cortical functions.	no	no
D	f	10 w	dtp-ipv-hib + pneu 1	1 d	2,5 d	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.	no	yes
E	m	14 m	mmr1 +menC	otitis 3d before	12 d	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.	no	yes

[a]   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.[27,28,73] 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.[23,74,75,76] 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. [23] 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. [50] Before, the Health Council published only a selection of reported adverse events. [77]

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. [78] 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. [79] 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. [80] 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.

    o   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.

    o   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.

    o   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.

- o 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. [80] 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. [77] 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. [81] 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. [82] 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

o   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.

o 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.

o 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. [86,87] 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.

o Abscess and superficial infection

Abscess at the injection site is an infrequent event. We have found no relation with abandonment of local disinfection procedures. [88] 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. [89] 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

o   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 off 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 that 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 hyper-tonicity 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.

o Fainting

Fainting or syncope is a common sequel of injections and thus of vaccinations as well. [100] 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. [101] 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). [102] 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. [11,72,103]

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 to acellular 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 discolouration occurs in a child that had collapse after previous of 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. [66,104105,106] 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]

    o   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. [110] 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. [111] 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.

    o   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 wrongfully.

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.

  o 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.

  o 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. [135,136,137] 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. [150,151,152] The most common symptoms appear to be urticarial rashes with or without swelling. See also below under urticarial rashes. [153,154,155]

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.

- o   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. [63,156,157,158]

o '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). [159] 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.

o 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. [160,161,162,163]

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-vaccinial 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. [67,116,117,121,122,123,125,164,165,166,167,168,169,170,171172,173] 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. [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)

- o   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]

- o   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]

- o   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]

- o   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]

 o 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]

 o 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 [208209,210,211,212] Especially with such non-specific or rare diagnoses other aetiologies should be kept in mind in order prevent harmful delay in intervention.

 o 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 spanisch 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]

 o 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]

 o 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. [27,28,50,51,188,189,241,242243]

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. [244] 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 HBIg. 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.

o   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.

o   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)

    o   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.)

    o   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.

- o   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.

- o   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.

o   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.

o   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.

o   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$\geq$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.

Acknowledgement

References

1   Vos D, Richardus JH. Het ontstaan van het Rijksvaccinatieprogramma, deel 1: De vroege jaren van vaccinatie in Nederland: 1823-1949. Infectieziekten Bulletin 2004; 15: 13-7

2   Vos D, Richardus JH. Het ontstaan van het Rijksvaccinatieprogramma, deel 2: Aanloop en totstandkoming van het RVP: 1949-1963. Infectieziekten Bulletin 2004; 15: 49-55

3   Verbrugge HP. The national immunization program of the Netherlands. Pediatrics 1990; 86: 1060-3

4   Hannik ChA, Verslag van de Geneeskundig Hoofdinspecteur over de vaccinatiecampagne tegen poliomyelitis gedurende de jaren 1957-62, 's Gravenhage: GHI; 1963

5   Lindner U, Blume SS. Vaccine Innovation and Adoption: Polio Vaccines in the UK, the Netherlands and West Germany, 1955–1965. Medical History 2006; 50: 425–446

6   Rümke HC, Vermeer-de Bondt PE, Labadie J. Vervroeging van vaccinatieschema en minder contra-indicaties in het Rijksvaccinatieprogramma. Tijdschr Jeugdgezondh 1999; 31: 2-5

7   Gezondheidsraad. Vaccinatie tegen kinkhoest (inclusief addendum).2004/04. Den Haag: Gezondheidsraad; 2004

8   GHI Bulletin. Preventie Hepatitis B bij pasgeborenen. Rijswijk: Staatstoezicht op de Volksgezondheid; 1989

9   Vermeer-de Bondt PE, Informatiebrochure voor professionals over Vaccinatie tegen Hepatitis B. Den Haag: VWS; 2003

10   Vermeer-de Bondt PE, Dzaferagic A, Maas van der NAT, Wesselo C, Phaff TAJ. Ervaringen met bijwerkingen van de eenmalige Meninigokokken C vaccinatie-campagne in 2002. Bilthoven: RIVM report 240082001; 2004

11   Klooster van't TM, Kemmeren JM, Vermeer-de Bondt PE, Oostvogels B, Phaff TAJ, Melker de HE, Maas van der NAT. Human papillomavirus vaccination catch-up campaign in 2009 for girls born in 1993 to 1996 in the Netherlands. Bilthoven: RIVM report 210012001; 2011

12   Gezondheidsraad. De toekomst van het Rijksvaccinatieprogramma: naar een programma voor alle leeftijden. 2007/02. Den Haag: Gezondheidsraad; 2007

13   Burgmeijer RJF, Hoppenbrouwers K, Handboek vaccinaties. Theorie en uitvoeringspraktijk. Assen: van Gorcum; 2011

14   Lier van EA, Oomen PJ, Giesbers H, Drijfhout IH, de Hoogh PAAM, Melker de HE, Vaccinatiegraad Rijksvaccinatieprogramma Nederland: Verslagjaar 2011. Bilthoven: RIVM report 210021014; 2011

15   Verbrugge HP. Youth Health Care in The Netherlands: a bird's eye view. Pediatrics 1990; 86: 1044-7

16   Rümke HC, Conyn-van Spaendonck MAE, Plantinga AD. Plan voor evaluatie van het Rijksvaccinatieprogramma. Bilthoven: RIVM report 213676001; 1994

17   Gezondheidsraad. Postmarketing Surveillance in Nederland. 1991/12. 1991. Den Haag: Gezondheidsraad; 1991

18   Broekmans AW, Lekkerkerker JFF, de Koning GHP, Vree PW. Nieuwe regels voor het melden van bijwerkingen in Nederland na 1995. Ned Tijdschr Geneeskd 1996; 140: 1166-67

19   WHO Collaborating Centre for International Drug Monitoring; 14th Annual Meeting of Participating National Centres. Barcelona: 1991

20   World Health Organization. Surveillance of Adverse Events Following Immunization: Field Guide for Managers of Immunization Programmes. WHO/EPI/TRAM/93.2. Geneva: WHO; 1991

21   Kohl KS, Bonhoeffer J, Chen R, Duclos P, Heijbel H, Heininger U, Loupi E. The Brighton Collaboration: enhancing comparability of vaccine safety data. Pharmacoepidemiol Drug Saf 2003; 4: 335-40

22   Macartney KK, Offit PA. How vaccine safety is monitored before and after licensure. Pediatr Ann 2001; 7: 392-9

23   Scheifel DW. Point, Couterpoint. Can Med Assoc J 1997; 157: 1705-06

24   Lopalco PL, Johansen K, Ciancio B, De Carvalho Gomes H, Kramarz P, Giesecke J, Monitoring and assessing vaccine safety: a European perspective. Bull World Health Organ 2004; 82: 828-35

25   Lankinen KS, Pastila S, Kilpi T, Nohynek H, Mäkelä PH, Olin P. Vaccinovigilance in Europe-need for timeliness, standardization and resources. Vaccine 2004; 22: 2071-2

26   Letourneau M, Wells G, Walop W, Duclos P. Improving global monitoring of vaccine safety: a survey of national centres participating in the WHO Programme for International Drug Monitoring. Pediatr Infect Dis J 2009; 28 Suppl 4: S97-S108

27   Chen RT. Vaccine risks: real, perceived and unknown. Vaccine 1999; 17 Suppl 3: S41-S46

28   Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? Lancet 1998; 351: 611-2

29   Fenichel GM. The pertussis vaccine controversy. The danger of case reports. Arch Neurol 1983; 40: 193-4

30   Baker, JP. The pertussis vaccine controversy in Great Britain, 1974-1986. Vaccine 2003; 21: 4003-10

31   Expanded Programme on Immunization (EPI); Lack of evidence that hepatitis B vaccine causes multiple sclerosis. Weekly Epidemiological Record 1997; 72: 149-56

32   Farez MF, Correale J. Immunizations and risk of multiple sclerosis: systematic review and meta-analysis. J Neurol 2011;258:1197-1206

33   Heijbel H, Chen RT, Dahlquist G. Cumulative incidence of childhood-onset IDDM is unaffected by pertussis immunization. Diabetes Care 1997; 20: 173-5

34   Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Childhood Vaccination and Type 1 Diabetes. N Engl J Med 2004; 350: 1398-1404

35   Lindberg B, Ahlfors K, Carlsson A, Ericsson UB, Landin OM, Lernmark A et al. Previous exposure to measles, mumps, and rubella-but not vaccination during adolescence-correlates to the prevalence of pancreatic and thyroid autoantibodies. Pediatrics 1999; 104: e12

36   Wakefield AJ, Murch SH, Anthony A, Linell J, Casson DM et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet 1998; 351: 637-41

37   Miller L, Reynolds J. Autism and Vaccination---The Current Evidence. J Spec Pediatr Nursing 2009; 14: 166-72

38   Coughlan S, Connell J, Cohen B, Jin L, Hall WW. Suboptimal measles-mumps-rubella vaccination coverage facilitates an imported measles outbreak in Ireland. Clin Infect Dis 2002; 35: 84-6

39   Hanratty B, Holt T, Duffell E, Patterson W, Ramsey M, White JM, Jin L, Litton P. UK measles outbreak in non-immune anthroposofic communities: the implication for the elimination of measles from Europe. Epidemiol Infect 2000; 125: 377-83

40   Muscat M. Who gets measles in Europe? J Infect Dis 2011; 204: S353-65

41   Vermeer-de Bondt PE, Maas NAT van der, Wesselo C, Dzaferagic A, Phaff TAJ. Adverse Events Following Immunization under the National Vaccination Programme of the Netherlands. Number IX-Reports in 2002. Bilthoven: RIVM report 000001009; 2004

42   Vermeer-de Bondt PE, Dzaferagic A, Maas NAT van der, Wesselo C, Phaff TAJ. Adverse Events Following Immunization under the National Vaccination Programme of the Netherlands. Number X-Reports in 2003. Bilthoven: RIVM report 240071001; 2004

43   Vermeer-de Bondt PE, Dzaferagic A, Wesselo C, Phaff TAJ, Maas NAT van der. Adverse Events Following Immunization under the National Vaccination Programme of the Netherlands. Number XI-Reports in 2004. Bilthoven: RIVM report 240071002; 2005

44   Maas NAT van der, Phaff TAJ, Wesselo C, Dzaferagic A, Vermeer-de Bondt PE. Adverse Events Following Immunization under the National Vaccination Programme of the Netherlands. Number XII-Reports in 2005. Bilthoven: RIVM report 240071003; 2006

45   Maas NAT van der, Phaff TAJ, Wesselo C, Vermeer-de Bondt PE. Adverse Events Following Immunization under the National Vaccination Programme of the Netherlands. Number XIII-Reports in 2006. Bilthoven: RIVM report 240071004; 2007

46   Maas NAT van der, Zonnenberg-Hoff IF, David S, Moorer N, Bults M, Wesselo C, et al. Adverse Events Following Immunization under the National Vaccination Programme of the Netherlands. Number XIV-Reports in 2007. Bilthoven: RIVM report 205021003; 2008

47   Maas NAT van der, Oostvogels B, Phaff TAJ, Wesselo C, Vermeer-de Bondt PE. Adverse Events Following Immunization under the National Vaccination Programme of the Netherlands. Number XV-Reports in 2008. Bilthoven: report 205021005; 2010

48   Maas NAT van der, Oostvogels B, Phaff TAJ, Wesselo C, Vermeer-de Bondt PE. Adverse Events Following Immunization under the National Vaccination Programme of the Netherlands; Number XVI-Reports in 2009. Bilthoven: RIVM report 205021008; 2010

49   Zhou W, Pool V, Iskander JK, English-Bullard R, Ball R, Wise RP, et al. Surveillance for safety after Immunizations: Vaccine Adverse Event Reporting System (VAERS)- United States, 1991-2001. In: Surveillance Summaries. MMWR 2003; 52 SS-1: 1-23

50   Vermeer-de Bondt PE, Labadie J, Rümke HC. Postvaccinale gebeurtenissen na toediening van RIVM-vaccins in het Rijksvaccinatieprogramma. Deel 1-meldingen in 1994. Bilthoven: RIVM rapport 100012001; 1997

51   Burgmeijer RJF, Bolscher DJA, Vermeer-de-Bondt PE, Labadie J, Rumke HC, Verhaaff C et al. Vaccinaties bij kinderen; uitvoering en achtergronden van het Rijksvaccinatieprogramma en andere vaccinaties bij kinderen. Assen: van Gorcum; 1998

52   Venulet J, Berkner GC, Cuicci AG eds. Assessing Causes of Adverse Drug Reactions. London: Academic press; 1982

53   Wassilak SG, Sokhey J. Monitoring of Adverse Events Following Immunization Programmes in the Expanded Programme on Immunization. WHO/EPI/GEN/91.2 Geneva: WHO; 1991

54   Kohl KS, Bonhoeffer J, Chen R, Duclos P, Heijbel H, Heininger U, et al. The Brighton Collaboration: enhancing comparability of vaccine safety data. Pharmacoepidemiol Drug Saf 2003; 4: 335-40

55   Bonhoeffer J, Kohl K, Chen R, Duclos P, Heijbel H, Heiniger U, et al. The Brighton Collaboration: addressing the need for standardised case definitions of adverse events following immunization (AEFI). Vaccine 2002; 21: 298-302

56   Gidudu J, Kohl KS, Halperin S, Hammer SJ, Heath PT, Hennig R, et al. The Brighton Collaboration Local Working Group. A local reaction at or near injection site: Case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2008; 26: 6800-13

57   Kohl KS, Walop W, Gidudu J, Ball L, Halperin S, Hammer SJ, at al. The Brighton Collaboration Local Reactions Working Group. Induration at or near injection site: Case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007; 25: 5839-57

58   Rothstein E, Kohl KS, Ball L, Halperin SA, Halsey N, Hammer SJ, at al. Brighton Collaboration Local Reaction Working Group. Nodule at injection site as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004; 22: 575-85

59   Marcy SM, Kohl KS, Dagan R, Nalin D, Blum M, Jones MC, et al. The Brighton Collaboration Fever Working Group. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004; 22: 551-6

60   Tapiainen T, Prevots R, Izurieta HS, Abramson J, Bilynsky R, Bonhoeffer J, et al. The Brighton Collaboration Aseptic Meningitis Group. Aseptic meningitis: Case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007; 25: 5893-802

61   Wise PW, Bonhoeffer J, Beeler J, Donato H, Downie P, Matthews D, et al. The Brighton Collaboration Thrombocytopenia Working Group. Thrombocytopenia: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007; 25: 5717-2

62   Bonhoeffer J, Vermeer P, Halperin S, Kempe A, Music S, Shindman J, et al. The Brighton Collaboration Persisitent Crying Working Group. Persistent crying in infants and children as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2004; 22: 586-91

63   Beigel J, Kohl KS, Khuri-Bulos N, Bravo L, Nell P, Marcy SM, et al. The Brighton Collaboration Rash Working Group. Rash including mucosal involvement: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007; 25: 5697-706

64   Kemmeren J, Vermeer-de Bondt PE, van der Maas NAT, Discoloured legs after vaccination-descriptive epidemiology. Eur J Pediatr 2009; 168: 43-50

65   Buettcher M, Heininger u, Braun M, Bonhoeffer J, Halperin S, Heijbel H, et al. The Brighton Collaboration HHE Working Group. Hypotonic-hyporesponsive episode (HHE) as an adverse event following immunization in early childhood: Case definition and guidelines for data collection, analysis, and presentation. Vaccine 2007; 25: 5875-81

66   Bonhoeffer J, Menkes J, Gold MS, de Souza-Brito G, Fisher MC, Halsey N, et al. The Brighton Collaboration Seizure Working Group. Generalized convulsive seizure as an adverse event following immunization: case definition and huidelines for data collection, analysis, and presentation. Vaccine 2004; 22: 557-62

67   Sejvar JJ, Kohl KS, Bilynsky R, Blumberg D, Cvetkovich T, Galama J, et al. The Brighton Collaboration Encephalitis Working Group. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007; 25: 5771-92

68   Erlewyn-Lajeunesse M, Bonhoeffer J, Ruggeberg JU, Heath PT. Anaphylaxis as an adverse event following immunisation. J Clin Pathol 2007; 60: 737-9
Brown SG, Mullins RJ, Gold MS. Anaphylaxis: diagnosis and management. Med J Aust. 2006; 185: 283-9

69   Klooster TM, Kemmeren JM, de Melker HE, Vermeer-de Bondt PE, van der Maas NAT. Two doses of pandemic influenza A(H1N1) vaccine: Tolerability in healthy young children in the Netherlands.Hum Vaccin 2011; 7: Oct Epub ahead of print

70   Folkenberg M, Callréus T, Svanström H, Valentiner-Branth P, Hviid A. Spontaneous reporting of adverse events following immunisation against pandemic influenza in Denmark November 2009-March 2010. Vaccine 2011; 29: 1180-4

71   Bonhoeffer J, Bentsi-Entchill A, Chen B, Fisher M, Gold M, Hartman K, et al. The Brigton Collaboration Methods Working Group. General Guidelines for Collection, Analysis and Presentations of Vaccine Safety Data in Surveillance Systems. Brighton Collaboration Homepage: www.brightoncollaboration.org

72   Klooster van 't TM, Kemmeren JM, Vermeer-de Bondt PE, Oostvogels B, Phaff TAJ, Melker de HE, et al. Adverse events following vaccination against human papillomavirus; results of the 2010 campaign in the Netherlands. Bilthoven: RIVM Letter report 210012002; 2011

73   Heininger U. The success of immunization-shoveling its own grave? Vaccine 2004; 22: 2071-2

74   Ball R. Methods of ensuring vaccine safety. Expert Rev Vaccines 2002; 2: 161-8

75   Halsey N. The science of evaluation of adverse events associated with vaccination. Semin Pediatr Infect Dis 2002; 13: 205-14

76   Siegrist CA. Mechanisms underlying adverse reactions to vaccines.J Comp Pathol 2007; 137 Suppl 1: S46-50

77   Gezondheidsraad. Verslag inzake ongewenste bijwerkingen vaccins Rijksvaccinatieprogramma in 1984. Advies no 1985/25. Den Haag: Gezondheidsraad; 1985

78   Hannik CA, Cohen H. Pertussis vaccine experience in the Netherlands. In: Manclark CR, Hill JC, eds. Proceedings of the third international symposium on pertussis, Bethesda, 1978. Washington: DHEW Publications 1979;279-82

79   Rümke HC. Contra-indicaties tegen vaccinaties van het Rijksvaccinatieprogramma. Ned Tijdschr Geneeskd 1989; 133: 1975-7

80   David S, Vermeer-de Bondt PE, van der Maas NA. Reactogenicity of infant whole cell pertussis combination vaccine compared with acellular pertussis vaccines with or without simultaneous pneumococcal vaccine in the Netherlands. Vaccine 2008; 26: 5883-7

81   Rümke HC. Vaccinaties en Bijwerkingen Symposium 2011 NVAMM. http://nvamm.nl/attachments/article/129/NVAMM-Rumke-17feb11.pdf

82   Rijkers GT, Vermeer-de Bondt PE, Spanjaard L, Breukels MA, Sanders EA. Return of Haemophilus influenzae type b infections. Lancet 2003; 361: 1563-4

83   Whelan J, van Binnendijk R, Greenland K, Fanoy E, Khargi M, Yap K, et al. Ongoing mumps outbreak in a student population with high vaccination coverage, Netherlands, 2010. Euro Surveill 2010; 15. pii: 19554

84   Netterlid E, Bruze M, Hindsén M, Isaksson M, Olin P. Persistent itching nodules after the fourth dose of diphtheria-tetanus toxoid vaccines without evidence of delayed hypersensitivity to aluminium. Vaccine 2004; 22: 3698-706

85   Frederiksen MS, Tofte H. Immunisation with aluminium-containing vaccine of a child with itching nodule following previous vaccination. Vaccine 2004; 23: 1-2

86   David S, Vermeer-de Bondt P, van der Maas N. [Increase in local symptoms in 4-year-olds following revaccination with DaPT-IPV]. Ned Tijdschr Geneeskd 2010; 154: A980, in Dutch

87   Kemmeren JM, Timmer SS, van der Maas NA, de Melker HE. Comparison of the tolerability of an acellular pertussis-containing vaccine given as the fifth booster dose in differently primed children. Vaccine 2011; 29: 4373-7

88   Werkgroep Infectiepreventie. Infectiepreventie in het Consultatiebureau Jeugdgezondheidszorg (JGZ). Leiden: WIP; 2007, www.WIP.nl, november 2011

89   Katz LD. Vaccination-induced myositis with intramuscular sterile abscess formation. Skeletal Radiol 2011; 40: 1099-101

90   Hannik CA. Surveillance of Reactions to Biologicals, commentary. Bull World Health Organ 1977; 55 Suppl 2: 163–5

91   Hopper JMH. Illness after whooping cough vaccination. Med Officer 1961; 106: 241

92   Braun MM, Terracciano G, Salive ME, et al. Report on a US public health service workshop on hypotonic-hyporesponsive episode (HHE) after pertussis vaccination. Pediatrics 1998; 102: e52

93   Bonhoeffer J, Gold MS, Heijbel H, Vermeer P., Blumberg D, Braun M, et al. Hypotonic-Hyporesponsive Episode (HHE) as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2004; 22: 563-8

94   Vermeer-de Bondt PE, Dzaferagić A, David S, van der Maas NA. Performance of the Brighton collaboration case definition for hypotonic-hyporesponsive episode (HHE) on reported collapse reactions following infant vaccinations in the Netherlands. Vaccine 2006; 24: 7066-70

95   Vermeer-de Bondt PE, van der Maas NA. The effect of age and dose number on the risk of collapse (hypotonic-hyporesponsive episode) after pertussis vaccination. Pediatr Infect Dis J 2008; 27: 355-7

96   Vermeer-de Bondt PE, Labadie J, Rümke HC. Rate of recurrent collapse after vaccination with whole cell pertussis vaccine: follow up study. BMJ 1998; 316: 902-3

97   Miller E. Collapse reactions after whole cell pertussis vaccination. BMJ 1998; 316: 876

98   Hannik CA, Cohen H. Changes in Plasma Insulin Concentration and Temperature of Infants after Pertussis Vaccination. Proceedings of the third International Symposium on Pertussis, Bethesda USA. DHEW Publ. 79-1830, 1979; 297-9

99   Blumberg DA, Mink CM, Lewis K, Chatfield P, Leach C, Smith LP, et al. Pathophysiology of reactions associated with pertussis vaccine. Dev Biol Stand 1991; 73: 289-95

100   Braun MM, Patriarca PA, Ellenberg SS. Syncope after immunization. Arch Pediatr Adolesc Med 1997; 151: 255-9

101   Vermeer-de Bondt PE, van 't Klooster TM, van der Maas NAT, de Melker HE. Syncope in mass vaccination campaigns in the Netherlands; MenC in 2002, HPV in 2009 and H1N1 in 2009. Den Haag: ESPID; 2011

102   Maas van der NAT, Vermeer-de Bondt PE, Hoefnagel J, van der Veen Y, van der Velde MW. [Immediate adverse events in the MenC catch up campaign of 2002]. Bilthoven: RIVM report 205051003; 2011, in Dutch

103   Callréus T, Svanström H, Nielsen NM, Poulsen S, Valentiner-Branth P, Hviid A. Human papillomavirus immunisation of adolescent girls and anticipated reporting of immune-mediated adverse events. Vaccine; 27: 2954-8

104   Hirtz DG, Nelson KB, Ellenberg JH. J Pediatr. Seizures following childhood immunizations. J Pediatr 1983; 102:14-8

105   Davis RL, Barlow W. Placing the risk of seizures with pediatric vaccines in a clinical context. Paediatr Drugs. 2003; 5: 717-22

106   Cendes F, Sankar R. Vaccinations and febrile seizures. Epilepsia 2011; 52 Suppl 3: 23-5

107   Verbeek NE, van Kempen M, Gunning WB, Renier WO, Westland B, Lindhout D, et al. Adults with a history of possible Dravet syndrome: an illustration of the importance of analysis of the SCN1A gene. Epilepsia. 2011; 52: e23-5

108   Spiczak von S, Helbig I, Drechsel-Baeuerle U, Muhle H, van Baalen A, van Kempen MJ, et al. A retrospective population-based study on seizures related to childhood vaccination. Epilepsia. 2011; 52: 1506-12

109   McIntosh AM, McMahon J, Dibbens LM, Iona X, Mulley JC, Scheffer IE, et al. Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. Lancet Neurol 2010; 9: 592-8

110   Østergaard JR. Febrile seizures. Acta Paediatr 2009; 98: 771-3

111   Strengell T, Uhari M, Tarkka R, Uusimaa J, Alen R, Lautala P, et al. Antipyretic agents for preventing recurrences of febrile seizures: randomized controlled trial. Arch Pediatr Adolesc Med 2009; 163: 799-804

112   Nelson KB, Ellenberg JH. Predisposing and causative factors in childhood epilepsy. Epilepsia 1987; 28 Suppl 1: S16-24

113   Barlow WE, Davis RL, Glasser JW, Rhodes PH, Thompson RS, Mullooly JP, et al. Centers for Disease Control and Prevention Vaccine Safety Datalink Working Group. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med 2001; 345: 656-61

114   Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, at al. Vaccine Safety Datalink. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics 2010; 126: e1-8

115   Huang WT, Gargiullo PM, Broder KR, Weintraub ES, Iskander JK, Klein NP, et al. Vaccine Safety Datalink Team. Lack of association between acellular pertussis vaccine and seizures in early childhood. Pediatrics 2010; 126: 263-9

116   Ward KN, Bryant NJ, Andrews NJ, Bowley JS, Ohrling A, Verity CM, et al. Risk of serious neurologic disease after immunization of young children in Britain and Ireland. Pediatrics 2007; 120: 314-21

117   Cherry JD, Shields WD. Recurrent seizures after diphtheria, tetanus, and pertussis immunization. Cause and effect v temporal association. Am J Dis Child. 1984; 138: 904-7

118   AMA Ad Hoc Panel on Pertussis Vaccine Injury. Pertussis vaccine injury. JAMA 1985; 254: 3083-4

119   Barkin RM, Jabhour JT, Samuelson JS. Immunizations, seizures, and subsequent evaluation. JAMA 1987; 258: 201

120   Baraff LJ, Shields WD, Beckwith L, Strome G, Marcy SM, Cherry JD, et al. Infants and children with convulsions and hypotonic-hyporesponsive episodes following diphtheria-tetanus-pertussis immunization: follow-up evaluation. Pediatrics 1988; 81: 789-94

121   Brown NJ, Berkovic SF, Scheffer IE. Vaccination, seizures and 'vaccine damage'. Curr Opin Neurol 2007; 20: 181-7

122   Stephenson JB. Pertussis immunisation convulsions are not evidence of encephalopathy. Lancet. 1979; 8139: 416-7

123   Shorvon S, Berg A. Pertussis vaccination and epilepsy--an erratic history, new research and the mismatch between science and social policy. Epilepsia 2008; 49: 219-25

124   Howson CP, Fineberg HV. Adverse events following pertussis and rubella vaccines. Summary of a report of the Institute of Medicine. JAMA 1992; 267: 392-6

125   Stephenson JBP. A Neurologist Looks at Neurological Disease Temporally related to DTP Immunization. Tokai J Exp Clin Med 1988; 13 (suppl): 157-64

126   Jacobson V, Nielsen C, Buch D, Shields WD, Christenson P, Zachau-Christiansen B, et al. Relationship of pertussis immunization to the onset of epilepsy, febrile convulsions and

central nervous system infections: a retrospective epidemiologic study. Tokai J Exp Clin Med 1988; 13 (Suppl): 137-42

127 Goodman M, Lamm SH, Bellman MH. Temporal relationship modelling: DTP or DT immunizations and infantile spasms. Vaccine. 1998; 16: 225-31

128 Kohl KS, Magnus M, Ball R, Halsey N, Shadomy S, Farley TA. Applicability, reliability, sensitivity, and specificity of six Brighton Collaboration standardized case definitions for adverse events following immunization. Vaccine 2008; 26: 6349-60

129 Nyman R, Peltola H. [Persistent crying -- central nervous reaction to triple vaccine]. Duodecim 1980; 96: 846-9 [Article in Finnish]

130 Feery BJ. Incidence and type of reactions to triple antigen (DTP) and DT (CDT) vaccines. Med J Aust 1982; 2: 511-5

131 Pan American Health Organization PAHO. Expanded Program on Immunization EPI. Immunization Practices Advisory Committee. Contraindications to pertussis vaccine. EPI Newsl 1984; 6: 1-2

132 Cody CL, Baraff LJ, Cherry JD, Marcy SM, Manclark CR. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. Pediatrics 1981; 68: 650-60

133 Verschoor PL, Wilschut JT, de Jonge GA, Kostense PJ. Frequent symptoms after DTPP vaccinations. Arch Dis Child 1991; 66: 1408-12

134 Jefferson T, Rudin M, Di Pietrantonj C. Adverse events after immunisation with aluminium-containing DTP vaccines: systematic review of the evidence. Lancet Infect Dis 2004; 4: 84-90

135 Reijneveld SA, Hirasing RA, Tjon A Ten W, Jonker PJ, Tjon A Ten WE, Brand PLP, et al. Huildagboek bij zuigelingen; een nuttig hulpmiddel om onderscheid te maken tussen normaal en excessief huilgedrag. Ned Tijdschr Geneeskd 2004; 148: 754-6

136 Long T. Excessive infantile crying: a review of the literature. J Child Health Care 2001; 5: 111-6

137 Rümke HC, Visser HK. [Childhood vaccinations anno 2004. II. The real and presumed side effects of vaccination]. Ned Tijdschr Geneeskd 2004; 148: 364-71 [Article in Dutch]

138 Blumberg DA, Mink CM, Lewis K, Chatfield P, Leach C, Smith LP, et al. Pathophysiology of reactions associated with pertussis vaccine. Dev Biol Stand 1991; 73: 289-95

139 Baraff LJ, Manclark CR, Cherry JD, Christenson P, Marcy SM. Analyses of adverse reactions to diphtheria and tetanus toxoids and pertussis vaccine by vaccine lot, endotoxin content, pertussis vaccine potency and percentage of mouse weight gain. Pediatr Infect Dis J 1989; 8: 502-7

140 Babl FE, Lewena S, Brown L. Vaccination-related adverse events. Pediatr Emerg Care 2006; 22: 514-9 [quiz 520-2]

141 Uberall MA, Stehr K, Cherry JD, Heininger U, Schmitt-Grohé S, Laussucq S, et al. The Pertussis Vaccine Study Group. Severe adverse events in a comparative efficacy trial in Germany in infants receiving either the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine, the Lederle whole-cell component DTP (DTP) or DT vaccine. Dev Biol Stand 1997; 89: 83-9

142 Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. N Engl J Med 1996; 334: 349-55

143 David S, Vermeer-de Bondt PE, van der Maas NA. Reactogenicity of infant whole cell pertussis combination vaccine compared with acellular pertussis vaccines with or without simultaneous pneumococcal vaccine in the Netherlands. Vaccine 2008 ; 26: 5883-7

144 Baraff LJ, Cherry JD, Cody CL, Marcy SM, Manclark CR. DTP vaccine reactions: effect of prior reactions on rate of subsequent reactions. Dev Biol Stand 1985; 61: 423-8

145 Blumberg DA, Morgan CA, Lewis K, Leach C, Holtzman A, Levin SR, at al. An ongoing surveillance study of persistent crying and hypotonic-hyporesponsive episodes following routine DTP immunization: a preliminary report. Tokai J Exp Clin Med 1988; 13 Suppl133-6

146 Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007; 25: 5675-84

147 Gold MS, Gidudu J, Erlewyn-Lajeunesse M, Law B; Brighton Collaboration Working Group on Anaphylaxis. Can the Brighton Collaboration case definitions be used to improve the quality of Adverse Event Following Immunization (AEFI) reporting? Anaphylaxis as a case study. Vaccine. 2010; 28: 4487-98

148 Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 2001; 56: 813–24

149 Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey

RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 2004; 113: 832–6

150   Fasano MB, Wood RA, Cooke SK, Sampson HA. Egg hypersensitivity and adverse reactions to measles, mumps, and rubella vaccine. J Pediatr 1992; 120: 878-81

151   Aickin R, Hill D, Kemp A.Measles immunisation in children with allergy to egg. BMJ 1994; 309: 223–5

152   James JM, Zeiger RS, Lester MR, Fasano MB, Gern JE, Mansfield LE, Schwartz HJ, et al. Safe administration of influenza vaccine to patients with egg allergy. J Pediatr 1998; 133: 624-8

153   James JM, Burks AW, Roberson PK, Sampson HA. Safe administration of the measles vaccine to children allergic to eggs. N Engl J Med 1995; 332: 1262-6

154   Gagnon R, Primeau MN, Des Roches A, Lemire C, Kagan R, Carr S, et al. PHAC-CIHR Influenza Research Network. Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine. J Allergy Clin Immunol 2010; 126: 317-23

155   Hawkes CP, Mulcair S, Hourihane JO. Is hospital based MMR vaccination for children with egg allergy here to stay? Ir Med J 2010; 103: 17-9

    Denning DW, Peet L, Poole J. Skin rash after triple vaccine. Arch Dis Child 1987; 62: 510-1

157   Bellón T, Blanca M. The innate immune system in delayed cutaneous allergic reactions to medications. Curr Opin Allergy Clin Immunol 2011; 11: 292-8

158   Babl FE, Lewena S, Brown L. Vaccination-related adverse events. Pediatr Emerg Care 2006; 22: 514-9

159   Kroesbergen HT, Moret-Huffmeijer L, Vermeer-de Bondt PE. [Events after simultaneous MMR and Meningococcal C vaccine. Tijdschr Soc Gezondh 2005; 83: 425-31, in Dutch

160   Grüber C, Warner J, Hill D, Bauchau V. EPAAC Study Group. Early atopic disease and early childhood immunization--is there a link? Allergy 2008; 63: 1464-72

161   Anderson HR, Poloniecki JD, Strachan DP, Beasley R, Björkstén B, Asher MI. ISAAC Phase 1 Study Group. Immunization and symptoms of atopic disease in children: results from the International Study of Asthma and Allergies in Childhood. Am J Public Health 2001; 91: 1126-9

162   Martignon G, Oryszczyn MP, Annesi-Maesano I. Does childhood immunization against infectious diseases protect from the development of atopic disease? tr Allergy Immunol 2005; 16: 193-200

163   Frydenberg AR, Buttery JP, Royle J. Determining the rate of varicella vaccine rash in children with moderate-severe eczema. J Paediatr Child Health 2005; 41: 561-3

164   Miller D, Wadsworth J, Ross E. Severe neurological illness: further analyses of the British National Childhood Encephalopathy Study. Tokai J Exp Clin Med 1988; 13 Suppl: 145-55

165   Griffith AH. Permanent brain damage and pertussis vaccination: is the end of the saga in sight? Vaccine 1989; 7: 199-210

166   Golden GS. Pertussis vaccine and injury to the brain. J Pediatr 1990; 116: 854-61

167   Cowan LD, Griffin MR, Howson CP, Katz M, Johnston RB Jr, Shaywitz BA, et al. Acute encephalopathy and chronic neurological damage after pertussis vaccine.Vaccine 1993; 11: 1371-9

168   Gale JL, Thapa PB, Wassilak SG, Bobo JK, Mendelman PM, Foy HM. Risk of serious acute neurological illness after immunization with diphtheria-tetanus-pertussis vaccine. A population-based case-control study. JAMA 1994; 271: 37-41

169   Moore DL, Le Saux N, Scheifele D, Halperin SA; Members of the Canadian Paediatric Society/Health Canada Immunization Monitoring Program Active (IMPACT). Lack of evidence of encephalopathy related to pertussis vaccine: active surveillance by IMPACT, Canada, 1993-2002. Pediatr Infect Dis J 2004; 23: 568-71

170   Kahane P, Arzimanoglou A. [Vaccine encephalopathy: a myth collapses?]. Presse Med. 2007 Oct;36(10 Pt 1):1339-40, in French

171   Neville B. Dravet syndrome and 'immunization encephalopathy'. Dev Med Child Neurol 2010; 52: 590-1

172   Pahud BA, Rowhani-Rahbar A, Glaser C, Gavali S, Salibay CJ, Fireman B, et al. Lack of association between childhood immunizations and encephalitis in California, 1998-2008. Vaccine 2011 Nov 10. [Epub ahead of print]

173   Reyes IS, Hsieh DT, Laux LC, Wilfong AA. Alleged Cases of Vaccine Encephalopathy Rediagnosed Years Later as Dravet Syndrome. Pediatrics 2011 Aug 15. [Epub ahead of print]

174   Mäkelä A, Nuorti JP, Peltola H. Neurologic disorders after measles-mumps-rubella vaccination. Pediatrics. 2002 Nov;110(5):957-63.

175   AD Stratton K, Ford A, Rusch E, Walford T, McLeod W, Hare H, Pryzbocki A, Martinez RN. Adverse Effects of Vaccines. Evidence and Causality. Institute of Medicine of the National Academies. National Academy of Science, Washington D.C. 2011

176   Jorch G, Tapiainen T, Bonhoeffer J, Fischer TK, Heininger U, Hoet B, et al. Brighton Collaboration Unexplained Sudden Death Working Group. Unexplained sudden death,

including sudden infant death syndrome (SIDS), in the first and second years of life: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007; 25: 5707-16

177   Hoffman HJ, Hunter JC, Damus K *et al*. Diphterheris-Tetanus-Pertussis Immunization and Sudden Infant Death: Results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of Sudden Infant Death Syndrome Risk Factors. Pediatrics 1987; 79: 598-611

178   Griffin MR, Ray WA, Livengood JR, Schaffner W. Risk of sudden infant death syndrome after immunization with the diphtheria-tetanus-pertussis vaccine. N Engl J Med 1988; 319: 618-23

179   Fleming PJ, Blair PS, Platt MW, Tripp J, Smith IJ, Golding J . The UK accelerated immunisation programme and sudden unexpected death in infancy: case-control study. BMJ 2001; 322: 822

180   Mitchell EA, Stewart AW, Clements M. Immunisation and the sudden infant death syndrome. New Zealand Cot Death Study Group. Arch Dis Child 1995; 73: 498-501

181   Jonville-Bera AP, Autret-Leca E, Barbeillon F, Paris-Llado J. The French Reference centers for SIDS. Sudden unexpected death in infants under 3 months of age and vaccination status – a case-control study. Br J Clin Pharmacol 2001; 51: 271-276

182   Vennemann MMT , Butterfass-Bahloul T, Jorch G. et al. Sudden infant death syndrome: No increased risk after immunisation. Vaccine 2007; 25: 336-40

183   Nieminen U, Peltola H, Syrjälä MT, Mäkipernaa A, Kekomäki R. Acute thrombocytopenic purpura following measles, mumps and rubella vaccination. A report on 23 patients. Acta Paediatr 1993; 82: 267-70

184   Miller E, Waight P, Farrington CP, Andrews N, Stowe J, Taylor B. Idiopathic thrombocytopenic purpura and MMR vaccine. Arch Dis Child 2001; 84: 227-9

185   France EK, Glanz J, Xu S, Hambidge S, Yamasaki K, Black SB, Marcy M, Mullooly JP, Jackson LA, Nordin J, Belongia EA, Hohman K, Chen RT, Davis R. Risk of Immune Thrombocytopenic Purpura after Measles-Mumps-Rubella Immunization in Children. For the Vaccine Safety Datalink Team. Pediatrics 2008; 121: e687-92

186   Andrews N, Stowe J, Miller E, Svanström H, Johansen K, Bonhoeffer J, et al. The VAESCO consortium. A collaborative approach to investigating the risk of thrombocytopenic purpura after measles-mumps-rubella vaccination in England and Denmark. Vaccine 2011 Jun 20 [Epub ahead of print]

187   Chen RT, Pless R, Destefano F. Epidemiology of autoimmune reactions induced by vaccination. J Autoimmun 2001; 16: 309-18

188   Schattner A. Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines. Vaccine 2005; 23: 3876-86

189   Siegrist CA. Autoimmune diseases after adolescent or adult immunization: what should we expect? CMAJ. 2007 Nov 20;177(11):1352-4

190   Siegrist CA, Lewis EM, Eskola J, Evans SJ, Black SB. Human papilloma virus immunization in adolescent and young adults: a cohort study to illustrate what events might be mistaken for adverse reactions. Pediatr Infect Dis J 2007; 26: 979–984

191   Stratton KR, Howe CJ, Johnston RB Jr. Adverse events associated with childhood vaccines other than pertussis and rubella. Summary of a report from the Institute of Medicine. JAMA 1994; 271: 1602-5

192   Graves PM, Barriga KJ, Norris JM, Hoffman MR, Yu L, Eisenbarth GS, et al. Lack of association between early childhood immunizations and beta-cell autoimmunity. Diabetes Care 1999; 22: 1694-7

193   Karvonen M, Cepaitis Z, Tuomilehto J. Association between type 1 diabetes and Haemophilus influenzae type b vaccination: birth cohort study. BMJ. 1999 May 1;318(7192):1169-72.

194   DeStefano F, Mullooly JP, Okoro CA, Chen RT, Marcy SM, Ward JI, et al. Vaccine Safety Datalink Team. Childhood vaccinations, vaccination timing, and risk of type 1 diabetes mellitus. Pediatrics 2001; 108: E112

195   Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Childhood vaccination and type 1 diabetes. N Engl J Med. 2004 Apr 1;350(14):1398-404

196   Immunization safety review Committee. Stratton K, Almario D, McCormick MC Eds. Immunization Safety review: Hepatitis B Vaccine and Demyelinating Neurological Disorders. IOM, 2002, ISBN 0-309-08469-5 Free executive summary: http://www.iom.edu/Reports/2002/Immunization-Safety-Review-Hepatitis-B-Vaccine-and-Demyelinating-Neurological-Disorders.aspx November 2011

197   Global Advisory Committee on Vaccine Safety, WHO. Response to the paper by MA Hernan and others in Neurology 14th September 2004 issue entitled "recombinant Hepatitis b Vaccine and the Risk of Multiple sclerosis". September 2004 at http://www.who.int/vaccine_safety/topics/hepatitisb/multiple_sclerosis/sep_04/en/index.html November 2011

198 Zonneveld-Huijssoon E, Ronaghy A, Van Rossum MA, Rijkers GT, van der Klis FR, Sanders EA, et al. Safety and efficacy of meningococcal c vaccination in juvenile idiopathic arthritis. Arthritis Rheum 2007; 56: 639-46

199 Heijstek MW, Pileggi GC, Zonneveld-Huijssoon E, Armbrust W, Hoppenreijs EP, Uiterwaal CS, et al. Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis. Ann Rheum Dis 2007; 66: 1384-7

200 Heijstek MW, Ott de Bruin LM, Bijl M, Borrow R, van der Klis F, Koné-Paut I, et al EULAR. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. Ann Rheum Dis 2011; 70: 1704-12

201 Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R, et al. Brighton Collaboration GBS Working Group. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2011 Jan 10;29(3):599-612.

202 Esteghamati A, Gouya MM, Keshtkar AA, Mahoney F. Relationship between occurrence of Guillain-Barre syndrome and mass campaign of measles and rubella immunization in Iranian 5-14 years old children. Vaccine 2008; 26: 5058-61

203 Haber P, Sejvar J, Mikaeloff Y, DeStefano F. Vaccines and Guillain-Barré syndrome. Drug Saf 2009;32: 309-23

204 Grimaldi-Bensouda L, Alpérovitch A, Besson G, Vial C, Cuisset JM, Papeix C, et al. The GBS-PGRx Study Group. Guillain-Barre syndrome, influenzalike illnesses, and influenza vaccination during seasons with and without circulating A/H1N1 viruses. Am J Epidemiol 2011; 174: 326-35

205 Maas van der NA, Kramer MA, Jacobs BC, van Soest EM, Dieleman JP, Kemmeren JM, et al. Guillain-Barré syndrome: background incidence rates in The Netherlands. J Peripher Nerv Syst 2011; 16: 243-9

206 Fenichel GM. Neurological complications of immunization. Ann Neurol 1982; 12: 119-28

207 Debeer P, De Munter P, Bruyninckx F, Devlieger R. Brachial plexus neuritis following HPV vaccination. Vaccine 2008; 26: 4417-9

208 Trump RC, White TR. Cerebellar ataxia presumed due to live, attenuated measles virus vaccine. JAMA 1967; 199: 129-30

209 Maas NAT van der, Vermeer-de Bondt PE, Melker H de, Kemmeren JM. Acute cerebellar ataxia in the Netherlands: A study on the association with vaccinations and varicella zoster infection. Vaccine 2009; 274: 1970-3

210 Benjamin CM, Chew GC, Silman AJ. Joint and limb symptoms in children after immunisation with measles, mumps, and rubella vaccine. BMJ 1992; 304: 1075-8

211 Plesner AM, Hansen FJ, Taudorf K, Nielsen LH, Larsen CB, Pedersen E. Gait disturbance interpreted as cerebellar ataxia after MMR vaccination at 15 months of age: a follow-up study. Acta Paediatr 2000; 89: 58-63

212 Miller E, Andrews N, Grant A, Stowe J, Taylor B. No evidence of an association between MMR vaccine and gait disturbance. Arch Dis Child 2005; 90: 292-6

213 Kilpi T, Nohynek H, Increased risk of narcolepsy observed among children and adolescents vaccinated with PandemrixR. National Institute for health and Welfare-KTL, Finland: 2011 Short address: http://www.thl.fi/doc/en/24103 November 2011

214 Bardage C, Persson I, Ortqvist A, Bergman U, Ludvigsson JF, Granath F. Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden. BMJ 2011; 343: d5956

215 Montastruc JL, Durrieu G, Rascol O. Pandemrix°, (H1N1)v influenza and reported cases of narcolepsy. Vaccine 2011; 29: 2010

216 Han F, Lin L, Warby SC, Faraco J, Li J, Dong SX, et al. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. Ann Neurol 2011; 70: 410-7

217 Vilensky JA, Foley P, Gilman S. Children and encephalitis lethargica: a historical review. Pediatr Neurol 2007; 37: 79-84

218 Stein DS, Blum NJ, Barbaresi WJ. Developmental and behavioral disorders through the life span. Pediatrics 2011; 128: 364-73

219 Offit PA. The power of 'box a'. Expert Rev Vaccines 2003; 2: 1-3

220 Kingsley JD, Varman M, Chatterjee A, Kingsley RA, Roth KS. Immunizations for patients with metabolic disorders. Pediatrics 2006; 118: e460-70

221 Klein NP, Aukes L, Lee J, Fireman B, Shapira SK, Slade B, Baxter R, Summar M. Evaluation of immunization rates and safety among children with inborn errors of metabolism. Pediatrics 2011; 127: e1139-46

222 Gale JL, Thapa PB, Wassilak SG, Bobo JK, Mendelman PM, Foy HM. Risk of serious acute neurological illness after immunization with diphtheria-tetanus-pertussis vaccine. A population-based case-control study. JAMA 1994; 271: 37-41

223   Farrington CP, Miller E, Taylor B. MMR and autism: further evidence against a causal association. Vaccine 2001; 19: 3632-5

224   Madsen KM, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, Thorsen P, et al. A population-based study of measles, mumps, and rubella vaccination and autism. N Engl J Med 2002; 347: 1477-82

225   Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Association between thimerosal-containing vaccine and autism. JAMA 2003; 290: 1763-6

226   DeStefano F, Thompson WW. MMR vaccine and autism: an update of the scientific evidence. Expert Rev Vaccines 2004; 3: 19-22

227   Hornig M, Briese T, Buie T, Bauman ML, Lauwers G, Siemetzki U, et al Lack of association between measles virus vaccine and autism with enteropathy: a case-control study. PLoS One 2008; 3: e3140

228   Offit PA, Quarles J, Gerber MA, Hackett CJ, Marcuse EK, Kollman TR, et al. Addressing parents' concerns: do multiple vaccines overwhelm or weaken the infant's immune system? Pediatrics 2002; 109: 124-9

229   Davidson M, Letson GW, Ward JI, Ball A, Bulkow L, Christenson P, et al. DTP immunization and susceptibility to infectious diseases. Is there a relationship? Am J Dis Child 1991; 145: 750-4

230   Gregson AL, Edelman R. Does antigenic overload exist? The role of multiple immunizations in infants. Immunol Allergy Clin North Am 2003; 23: 649-64

231   Joffe LS, Glode MP, Gutierrez MK, Wiesenthal A, Luckey DW, Harken L. Diphtheria-tetanus toxoids-pertussis vaccination does not increase the risk of hospitalization with an infectious illness. Pediatr Infect Dis J 1992; 11: 730-5

232   Griffin MR, Taylor JA, Daugherty JR, Ray WA. No increased risk for invasive bacterial infection found following Doiphtheria-tetanus-Pertussis Immunization. Pediatr 1992; 89: 640-2

233   Black SB, Cherry JD, Shinefield HR, Fireman B, Christenson P, Lampert D. Apparent decreased risk of invasive bacterial disease after heterologous childhood immunization. Am J Dis Child 1991; 145: 746-9

234   Miller E, Andrews N, Waight P, Taylor B. Bacterial infections, immune overload, and MMR vaccine. Measles, mumps, and rubella. Arch Dis Child 2003; 88: 222-3

235   Hviid A, Wohlfahrt J, Stellfeld M, Melbye M. Childhood vaccination and nontargeted infectious disease hospitalization. JAMA 2005; 294: 699-705

236   Aaby P, Benn CS. Non-specific and sex-differential effects of routine vaccines: what evidence is needed to take these effects into consideration in low-income countries? Hum Vaccin 2011; 7: 120-4

237   Shann, F. A little bit of measles does you good. BMJ 1999; 319: 4-5

238   Fine PE, Williams TN, Aaby P, Källander K, Moulton LH, Flanagan KL, et al. Working Group on Non-specific Effects of Vaccines. Epidemiological studies of the 'non-specific effects' of vaccines: I--data collection in observational studies. Trop Med Int Health 2009; 14: 969-76

239   Farrington CP, Firth MJ, Moulton LH, Ravn H, Andersen PK, Evans S; Working Group on Non-specific Effects of Vaccines. Epidemiological studies of the non-specific effects of vaccines: II--methodological issues in the design and analysis of cohort studies. Trop Med Int Health 2009; 14: 977-85

240   Halsey NA, Boulos R, Mode F, Andre J, Bowman L, Yaeger RG, et al. Response to measles vaccine in Haitian infants 6 to 12 months old. Influence of maternal antibodies, malnutrition, and concurrent illnesses. N Engl J Med 1985; 313: 544-9

241   Collet JP, MacDonald N, Cashman N, Pless R. Monitoring signals for vaccine safety: the assessment of individual adverse event reports by an expert advisory committee. Advisory Committee on Causality Assessment. Bull World Health Organ 2000; 78(2): 178-85

242   Williams SE, Klein NP, Halsey N, Dekker CL, Baxter RP, Marchant CD, et al. Overview of the Clinical Consult Case Review of adverse events following immunization: Clinical Immunization Safety Assessment (CISA) network 2004-2009. Vaccine 2011; 29(40): 6920-7

243   LaRussa PS, Edwards KM, Dekker CL, Klein NP, Halsey NA, Marchant C, et al. Understanding the role of human variation in vaccine adverse events: the Clinical Immunization Safety Assessment Network. Pediatrics 2011; 127 Suppl 1: S65-73

244   Lewis E, Shinefield HR, Woodruff BA, Black SB, Destefano F, Chen RT, Ensor R; Vaccine Safety Datalink Workgroup. Safety of neonatal hepatitis B vaccine administration. Pediatr Infect Dis J 2001;20(11):1049-54

List of Abbreviations

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

Appendix 1: Resume of Product Characteristics 2010

Vaccines in RVP	Producer	constituents	
DTP-IPV-Hib vaccine Diphtheria, acellular Pertussis, Tetanus and inactivated Poliomyelitis vaccine mixed with conjugated Hib-vaccine 0.5 ml	Aventis Pasteur RVG 32118	Diphtheria toxoid	≥ 30 IE
		Tetanus toxoid	≥ 40 IE
		Pertussis toxoid (PT)	20 µg
		Filamenteuze hemagglutinine (FHA)	20 µg
		Fimbriae agglutinogenen 2 and 3 (FIM)	5 µg
		Pertactin (PRN)	3 µg
		Inactivated poliovirus type 1 (Mahoney)	40 DE
		Inactivated poliovirus type 2 (MEF-1)	8 DE
		Inactivated poliovirus type 3 (Saukett)	32 DE
		Haemophilus influenzae type b polysaccharide	10 µg
		Conjugated to tetanus toxoid (PRP-T)	20 µg
DTP-IPV-Hib vaccine Diphtheria, acellular Pertussis, Tetanus and inactivated Poliomyelitis vaccine mixed with conjugated Hib-vaccine 0.5 ml	GSK RVG 22123	Diphtheria toxoid*	≥ 30 IE
		Tetanus toxoid*	≥ 40 IE
		Pertussis toxoid (PT)*	25 µg
		Filamenteuze hemagglutinine (FHA)*	25 µg
		Pertactin*	8 µg
		Inactivated poliovirus type 1	40 DE
		Inactivated poliovirus type 2	8 DE
		Inactivated poliovirus type 3	32 DE
		Haemophilus influenzae type b polysaccharide**	10 µg
		*adsorbed to aluminiumhydroxide	0.95 mg
		**conjugated to tetanus toxoid and absorbed to aluminium phosphate	1.45 mg
DTP-IPV-Hib-HepB vaccine Diphtheria, acellular Pertussis, Tetanus, inactivated Poliomyelitis and Hepatitis B vaccine mixed with conjugated Hib-vaccine 0.5 ml	GSK EU/1/00/152/001 EU/1/00/152/002 EU/1/00/152/003 EU/1/00/152/004 EU/1/00/152/005 EU/1/00/152/006 EU/1/00/152/007 EU/1/00/152/008	Diphtheria toxoid*	≥ 30 IE
		Tetanus toxoid*	≥ 40 IE
		Pertussis toxoid* (PT)	25 µg
		Filamenteuze hemagglutinine* (FHA)	25 µg
		Pertactin* (PRN)	8 µg
		Hepatitis-B**,***	10 µg
		Inactivated poliovirus type 1 (Mahoney)	40 DE
		Inactivated poliovirus type 2 (MEF-1)	8 DE
		Inactivated poliovirus type 3 (Saukett)	32 DE
		Haemophilus influenzae type b polysaccharide***	10 µg
		Conjugated to tetanus toxoid (PRP-T)	20-40 µg
		*adsorbed to aluminiumhydroxide	0.95 mg
		**produced in yeast (Saccharomyces cerevisiae) by recombinant DNA techniques	
		***adsorbed to aluminium phosphate	1.45 mg
DTP-IPV vaccine Diphtheria, Acellular Pertussis, Tetanus and inactivated Poliomyelitis vaccine 0.5 ml	Sanofi Pasteur RVG 27569	Diphtheria toxoid	≥ 2 IE
		Tetanus toxoid	≥ 20 IE
		Pertussis toxoid (PT)	2.5 µg
		Filamentous hemagglutinin (FHA)	5 µg
		Fimbriae 2 and 3 (FIM)	5 µg
		Pertactin (PRN)	3 µg
		Inactivated poliovirus type 1	40 DE
		Inactivated poliovirus type 2	8 DE
		Inactivated poliovirus type 3	32 DE
		adsorbed to aluminium phosphate	0.33 mg Al

DTP-IPV vaccine Diphtheria, acellular Pertussis, Tetanus and inactivated Poliomyelitis vaccine 0.5 ml	GSK RVG 28912	Diphtheria toxoid* Tetanus toxoid* Pertussis toxoid (PT)* Filamenteuze hemagglutinine (FHA)* Pertactin* Inactivated poliovirus type 1 Inactivated poliovirus type 2 Inactivated poliovirus type 3 *adsorbed to aluminiumhydroxide	≥ 30 IE $\geq$ 40 IE 25 µg 25 µg 8 µg 40 DE 8 DE 32 DE 0.95 mg
DT-IPV vaccine Diphtheria, Tetanus and inactivated Poliomyelitis vaccine 1 ml	NVI RVG 17641	Diphtheria toxoid * Tetanus toxoid* Inactivated poliovirus type 1 Inactivated poliovirus type 2 Inactivated poliovirus type 3 *adsorbed to aluminium phosphate	$\geq$ 5 IE $\geq$ 20 IE $\geq$ 20 DE $\geq$ 2 DE $\geq$ 3.5 DE 1.5 mg
Pneumococcal vaccine Pneumococcal conjugated vaccine absorbed with aluminiumfosfate 0.5 ml	Wyeth EU/1/00/167/001	Pneumococcal polysaccharide Serotype 4 Pneumococcal polysaccharide Serotype 6B Pneumococcal polysaccharide Serotype 9V Pneumococcal polysaccharide Serotype 14 Pneumococcal polysaccharide Serotype 18C Pneumococcal polysaccharide Serotype 19F Pneumococcal polysaccharide Serotype 23F Conjugated CRM_{197} and absorbed to aluminium phosphate	2 µg 4 µg 2 µg 2 µg 2 µg 2 µg 2 µg 0.5 mg
MMR vaccine Mumps, measles and rubella vaccine 0.5 ml	Sanofi Pasteur RVG 17672	Mumps virus Measles virus Rubella virus	$\geq$ 12.500 p.f.u. $\geq$ 1000 p.f.u. $\geq$ 1000 p.f.u.
MMR vaccine Mumps, measles and rubella vaccine 0.5 ml	GSK RVG 22052	Mumps virus Measles virus Rubella virus	$\geq$ 7500 p.f.u. $\geq$ 1000 p.f.u. $\geq$ 1000 p.f.u.
Meningococcal C vaccine Conjugated menC vaccine 0.5 ml	Baxter RVG 26343	Neisseria meningitidis (C!!-strain) Polysaccharide ()-deacetylated Conjugated to Tetanus toxoid Adsorbed to aluminium hydroxide	 10 µg 10-20 mg 0.5 mg Al^{3+}
Hepatitis B vaccine Hepatitis B vaccine for children 0.5 ml	GSK RVG 24290	Hepatitis B-virus surface antigen, recombinant* (HBsAg) 10 µg	

http://onderzoek.nvi-vaccin.nl/Bijsluiters/Bijsluiters_RVP

Appendix 2: Netherlands Vaccination Programme 2010

Rijksvaccinatieprogramma 2010

Richtlijn voor de uitvoering van vaccinaties tegen difterie, kinkhoest, tetanus, poliomyelitis, Hib-ziekte (ziekte veroorzaakt door *Haemophilus influenzae* type b), hepatitis B, bof, mazelen, rodehond, meningokokken C-ziekten, pneumokokkenziekten en HPV-infectie/baarmoederhalskanker.

Voor de implementatie van deze RVP-Richtlijn vindt u informatie in de Uitvoeringsregels RVP 2010 en de VaccInformatiemap (www.rivm.nl/cib/rvp)

Opmerkelijke wijzigingen ten opzichte van 2009:
- De vaccinatie tegen Hib-ziekte wordt beperkt tot de 2e verjaardag;
- De voor najaar 2009 aangekondigde opname van de HPV-vaccinatie in het RVP is door omstandigheden uitgesteld tot vooralsnog het voorjaar 2010, en geldt nu voor het hele geboortecohort 1997.

Overzicht van vaccinaties in 2010

Geboortejaar	Vaccinaties
2010	HepB-0* DKTP-Hib** en Pneu
2009	DKTP-Hib** en Pneu BMR en MenC
2006	DKTP
2001	DTP en BMR
1997***	HPV

* alleen voor kinderen van HBsAg-positieve moeders
** wordt vervangen door DKTP-Hib-HepB voor kinderen die in aanmerking komen voor een HepB-vaccinatie
Voor asielzoekerskinderen gelden aparte regels (zie 1.10)
*** alleen meisjes

1 Algemeen

1.1 Organisatie
De minister van VWS bepaalt de inhoud van het Rijksvaccinatieprogramma (RVP). In opdracht van de minister is het RIVM/Centrum Infectieziektebestrijding (CIb) verantwoordelijk voor de regie van het programma.
De uitvoering van het RVP wordt verzorgd door thuiszorgorganisaties, GGD'en, en verloskundig hulpverleners, onder verantwoordelijkheid en medisch toezicht van RIVM-Regionale Coördinatie Programma's (RIVM-RCP's). Het Nederlands Vaccin Instituut (NVI) is verantwoordelijk voor de vaccinvoorziening. Naast de controle, veiligheidsbewaking en evaluatie van het vaccinatieprogramma, coördineert het RIVM de communicatie over het RVP.

1.2 Vaccinatieschema per kind in 2010
Zie het schema bovenaan pagina 2.

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

rijksvaccinatieprogramma

Vaccinatieschema per kind in 2010

Leeftijd	Vaccinaties (regulier)	Vaccinaties (doelgroep HepB)
0 maanden (< 48 uur)		HepB-0[1]
2 maanden	DKTP-Hib-1 + Pneu-1	DKTP-Hib-HepB-1[2] + Pneu-1
3 maanden	DKTP-Hib-2 + Pneu-2	DKTP-Hib-HepB-2[2] + Pneu-2
4 maanden	DKTP-Hib-3 + Pneu-3	DKTP-Hib-HepB-3[2] + Pneu-3
11 maanden	DKTP-Hib-4 + Pneu-4	DKTP-Hib-HepB-4[2] + Pneu-4
14 maanden	BMR-1 + MenC	BMR-1 + MenC
4 jaar	DKTP-5	DKTP-5
9 jaar	DTP-6 + BMR-2	DTP-6 + BMR-2
12 -13 jaar	HPV-1[3] + HPV-2[3] + HPV-3[3]	HPV-1[3] + HPV-2[3] + HPV-3[3]

1 Alleen voor kinderen van HbsAg-positieve moeders
2 Alleen voor de in paragraaf 2 van deze richtlijn omschreven doelgroepen.
3 Alleen voor meisjes

Alle vaccins in het RVP moeten in beginsel volgens het in deze RVP-richtlijnen aangegeven schema worden toegediend. Afwijkingen van het schema vereisen de goedkeuring van de medisch adviseur van RIVM-RCP. Het is niet toegestaan de dosering van het vaccin te halveren, andere afwijkende doseringen of verdunningen toe te dienen en vaccins te mengen. Het effect hiervan op de werkzaamheid is onbekend en het leidt tevens niet tot minder bijwerkingen.

1.4 Onvolledig gevaccineerde kinderen
Kinderen die niet of niet volledig zijn gevaccineerd, kunnen tot 13 jaar de nog noodzakelijke vaccinaties, volgens de daartoe geldende inhaalschema's, kosteloos ontvangen in het kader van het RVP. Asielzoekerskinderen ontvangen de noodzakelijke vaccinaties tot 19 jaar. Daarbij gelden de volgende regels: zie schema

Voor het afmaken van onvolledige series zijn de meest recente schema's van toepassing. Informatie hierover vindt u in de Uitvoeringsregels RVP 2010 of u kunt contact opnemen met de medisch adviseur van het RIVM-RCP in uw werkgebied.

1.5 Registratie en verantwoording
De vaccinaties worden bij het RIVM-RCP door de uitvoerende organisatie verantwoord door inzending van de ingevulde oproepkaart; vervolgens registreert en beoordeelt RIVM-RCP de toegediende vaccinaties. Het is voor de uitvoerenden ook mogelijk de vaccinaties digitaal te registreren (RVP-Online).

Schema voor onvolledig gevaccineerde kinderen

Vaccinatie	Alleen voor kinderen:
Pneu	tot de 2e verjaardag
Hib	tot de 2e verjaardag
BMR-0	Asielzoekerskinderen op de leeftijd van 9 maanden een extra BMR
HepB	geboren op of na 1 januari 2003, op voorwaarde dat: • tenminste één ouder afkomstig is uit een land waar hepatitis B middel- of hoogendemisch is, • het een asielzoekerskind betreft, of • moeder HbsAg-positief is. met het syndroom van Down en geboren op of na 1 januari 2008
DKTP 4 jaar	die de volledige basisimmunisatie DKTP-Hib voor de tweede verjaardag hebben afgerond óf ter opbouw van basisimmuniteit
MenC	geboren op of na 1 juni 2001
HPV (alleen meisjes)	geboren op of na 1-1-1997

1.6 Financiële regels
De kosten van de uitvoering van het RVP komen ten laste van de AWBZ. De RIVM-RCP's ontvangen een bedrag per toegediende vaccinatie. De RIVM-RCP's dragen zorg voor de doorbetaling van de ter beschikking gestelde gelden aan de uitvoerende organisaties volgens landelijke richtlijnen.

②

rijksvaccinatieprogramma

Voor vaccinaties die in het kader van het RVP zijn uitgevoerd door de thuiszorg, GGD, verloskundig hulpverlener en ziekenhuizen betalen de ouders geen bijdrage. Als ouders kiezen voor een ander vaccin dan het vaccin dat door RIVM-RCP ter beschikking is gesteld, vervalt het recht op kosteloze verstrekking. Zij kunnen zich met hun wensen tot de huisarts wenden.

Ook voor vaccinaties, gegeven overeenkomstig het RVP, maar zonder tussenkomst van de RIVM-RCP's, worden geen gratis vaccins ter beschikking gesteld, noch enige vergoeding gegeven.

1.7 Tijdigheid vaccinaties

Het is van groot belang de vaccinaties volgens het geldende schema te geven. De in deze richtlijnen vermelde vaccinatieleeftijden in maanden of jaren zijn geen minimale leeftijden maar optimale leeftijden. De 1e vaccinatie krijgt een kind als het 6, 7, 8 of 9 weken oud is. In geval van de HepB-0-vaccinatie is tijdigheid (binnen 48 uur nà de geboorte) een noodzaak, omdat het hier post-expositie profylaxe betreft en geen preventie.

1.8 Vaccindistributie

Het Nederlands Vaccininstituut (NVI) levert de vaccins voor het Rijksvaccinatieprogramma aan de RIVM-RCP's. De RIVM-RCP's houden toezicht op de distributie en het gebruik van de vaccins. De uitvoerende instellingen krijgen uitsluitend vaccins na aanvraag bij de RIVM-RCP's. Vaccins worden verstrekt onder voorwaarde dat deze worden gebruikt voor de uitvoering van het RVP of, in bijzondere omstandigheden, volgens richtlijnen gegeven door of namens de minister van Volksgezondheid, Welzijn en Sport.

1.9 Vaccinbeheer

De RIVM-RCP's leveren de vaccins aan de uitvoerende instellingen. Vaccins worden opgeslagen en beheerd conform de vigerende Cold-Chainrichtlijnen van het RIVM-RCP.

Bij vaccinincidenten dient men altijd contact op te nemen met de RIVM-RCP's.

1.10 Asielzoekerskinderen

Asielzoekerskinderen kunnen de noodzakelijke vaccinaties ontvangen tot zij 19 jaar worden. Voor deze kinderen gelden aparte regels, met name met betrekking tot HepB en BMR-0, en (inhaal)schema's die te vinden zijn in de Uitvoeringsregels RVP. Asielzoekers hebben geen aanspraak op voorzieningen krachtens de AWBZ. Kosten voor vaccinaties van deze doelgroep worden vergoed door de regeling zorg asielzoekers (RZA).

2 Toelichting op vaccins en vaccinaties

2.1 Zuigelingen

DKTP (tegen difterie – kinkhoest - tetanus - poliomyelitis) – **Hib** (tegen ziekte veroorzaakt door *Haemophilus influenzae* type b)
Zuigelingen krijgen de DKTP-Hib-vaccinatie op de leeftijd van respectievelijk **2**, **3** en **4** maanden. Tussen de eerste drie vaccinaties dient een periode van **4** weken te zitten. De vierde DKTP-Hib-vaccinatie krijgen kinderen volgens schema op de leeftijd van **11** maanden.
In het RVP wordt in principe het DKTP-Hib-combinatievaccin gebruikt. Voor reeds DKTP-gevaccineerde kinderen, geboren op of na 1 april 1993, die formeel aanspraak hebben op Hib-vaccinatie en op latere leeftijd Nederland zijn binnengekomen, is separaat Hib-vaccin beschikbaar. Vanaf de leeftijd van 1 jaar volstaat één dosis. Als zij ook aanvullend tegen DKTP moeten worden gevaccineerd, is hiervoor na een eerste dosis met DKTP-Hib, DKTP-vaccin beschikbaar.

③

rijksvaccinatieprogramma

rijksvaccinatieprogramma

HepB-0 (tegen hepatitis B)
Voor deze vaccinatie komen kinderen van HbsAg-positieve moeders (draagsters van het hepatitis B-virus) in aanmerking. De verloskundig hulpverlener dient het hepatitis B-vaccin **binnen 48 uur na de geboorte** toe, liefst direct na het toedienen van de hepatitis B-immunoglobuline, maar in een ander ledemaat. Deze tijdigheid is noodzakelijk, omdat het hier post-expositie profylaxe betreft en geen preventie. Het RIVM-RCP verstrekt het vaccin.
Kinderen van HBsAg-positieve moeders krijgen vervolgens op de leeftijd van **2, 3, 4** en **11** maanden een hepatitis B-vaccinatie in de vorm van DKTP-Hib-HepB-vaccin; zie volgende paragraaf.

DKTP (tegen difterie – kinkhoest - tetanus - poliomyelitis) - **Hib** (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 ≥2%).[4]
2. Kinderen van HBsAg-positieve moeders (draagsters van het hepatitis B-virus).
3. Kinderen met het syndroom van Down, geboren op of na 1 januari 2008.
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 eerste drie vaccinaties dient een periode van 4 weken te zitten. De vierde DKTP-Hib-HepB-vaccinatie krijgen ze volgens schema op de leeftijd van **11** maanden.
Ad 2) Bij deze kinderen wordt de serie HepB-vaccinaties waarmee direct na de geboorte is begonnen (zie HepB-0), afgemaakt volgens het schema en de richtlijnen zoals hierboven vermeld onder ad 1. Omdat het hier postexpositieprofylaxe betreft en geen preventie, dient het schema van 0, 2, 3, 4 en 11 maanden bij deze kinderen strikt gevolgd te worden. Om te voorkomen dat het kind besmet raakt en zelf ook drager wordt, is uitstel van de HepB-vaccinatie niet toegestaan.
Ad 3) Idem als de categorie hierboven genoemd onder ad 1.

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

Pneu (tegen pneumokokkenziekte)
Op de leeftijd van 2, 3, 4, en 11 maanden krijgen kinderen een pneumokokkenvaccinatie. De Pneu-vaccinatie wordt simultaan (op dezelfde dag) met de DKTP-Hib of DKTP-Hib-HepB-vaccinatie gegeven, maar in een ander ledemaat.

BMR (tegen bof - mazelen - rodehond)
Op de leeftijd van 14 maanden krijgen kinderen de eerste BMR-vaccinatie.
Deze vaccinatie wordt simultaan (op dezelfde dag) met de MenC-vaccinatie toegediend, maar in een ander ledemaat.
Een asielzoekerskind krijgt de eerste (extra) vaccinatie op de leeftijd van 9 maanden (BMR-0).

[4] Wat betreft de prevalentie van dragerschap gaf de WHO een lijst van landen waar Hepatitis B laag-endemisch is, de zogenaamde negatieve landenlijst: Andorra, Australië, Bahamas, Barbados, België, Bermuda, Canada, Chili, Colombia, Costa Rica, Cuba, Cyprus, Denemarken, Duitsland, El Salvador, Estland, Finland, Frankrijk, Hongarije, Ierland, Luxemburg, Mexico, Monaco, Nederland, Nicaragua, Nieuw-Zeeland, Noorwegen, Oostenrijk, Paraguay, Peru, San Marino, Sri Lanka, Slowakije, Tsjechië, Uruguay, IJsland, Verenigd Koninkrijk, Verenigde Staten, Zweden en Zwitserland. Hoewel de epidemiologische situatie door het hepatitis B-vaccinatiebeleid in veel landen veranderd is en de WHO geen actualisering van de landenlijst meer publiceert, blijft de 'oude' landenlijst een bruikbare indicatie geven voor bepaling van de doelgroep voor hepatitis B-vaccinatie.

④
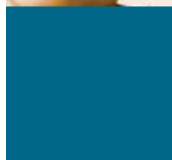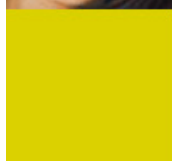
MenC (tegen meningokokken C-ziekte)
Op de leeftijd van 14 maanden krijgen kinderen de MenC-vaccinatie.
Deze vaccinatie wordt simultaan (op dezelfde dag) met de BMR-vaccinatie toegediend, maar in een ander ledemaat.

2.2 Kleuters

DKTP (Difterie - Kinkhoest - Tetanus - Poliomyelitis)
De in 2006 geboren kinderen worden in 2010 gerevaccineerd met DKTP-vaccin voor 4-jarigen.

2.3 Schoolkinderen

DTP (tegen difterie - tetanus - poliomyelitis)
Kinderen geboren in 2001 krijgen in 2010 een revaccinatie met DTP-vaccin.
Toediening van de DTP-vaccinatie gebeurt simultaan (op dezelfde dag) met de BMR-vaccinatie, maar in een ander ledemaat.

BMR (tegen bof - mazelen - rodehond)
Kinderen geboren in 2001 krijgen in 2010 de tweede BMR-vaccinatie.
Toediening van de BMR-vaccinatie gebeurt simultaan (op dezelfde dag) met de DTP-vaccinatie, maar in een ander ledemaat.

2.4 Adolescente meisjes

HPV tegen infectie door humaan papillomavirus ter preventie van baarmoederhalskanker
In 2010 komen meisjes geboren in 1997 in aanmerking voor HPV-vaccinatie in het RVP.

De vaccinatie bestaat uit een serie van drie doses met een schema 0, 1 en 6 maanden. Als men al eerder op eigen initiatief buiten het RVP één of twee doses HPV-vaccin heeft gehad, kan de serie niet worden afgemaakt binnen het RVP tenzij de eerdere vaccinaties met hetzelfde vaccin (Cervarix) zijn gegeven. De HPV-vaccins zijn namelijk niet onderling uitwisselbaar.

3 Simultane vaccinaties en registratie van partijnummers

Simultane vaccinaties zijn vaccinaties die op dezelfde dag worden toegediend, meestal gelijktijdig, maar in principe binnen 24 uur na elkaar. Deze toediening dient altijd in verschillende ledematen plaats te vinden.

Van elke gevaccineerde zuigeling en kleuter en schoolkind moet bekend zijn welk vaccin in welke ledemaat is toegediend. Dit is nodig voor de herkenning en duiding van (mogelijke) lokale bijwerkingen. Daarnaast dienen ook de partijnummers van toegediende vaccins geregistreerd te worden, zodat deze zo nodig te herleiden zijn naar individuele kinderen.

4 Bijwerkingen

Na vaccinaties kunnen bijwerkingen optreden. Meestal gaat het om niet ernstige, voorbijgaande verschijnselen. Voor een goede veiligheidsbewaking is melding van bijwerkingen van groot belang. Er wordt dan ook dringend verzocht elke ernstige, onverwachte of onrust veroorzakende (mogelijke) bijwerking te melden aan het RIVM/Centrum Infectieziektebestrijding te Bilthoven, onder vermelding van het partijnummer van het betreffende vaccin (tel. 030 274 24 24; fax 030 274 44 30; e-mail: libris@rivm.nl). Ook kunt u uw melding digitaal doen met het registratieformulier (zie www.rivm.nl/cib/rvp/).

5 Informatie RVP

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

RIVM-RCP Noord	Groningen / Friesland / Drenthe	050-368 6350	rcpnoord@rivm.nl
RIVM-RCP Oost	Overijssel / Gelderland	0570-661 520	rcpoost@rivm.nl
RIVM-RCP Midden-West	Utrecht / Noord-Holland / Flevoland	0346-550 040	rcpmiddenwest@rivm.nl
RIVM-RCP Zuid-West	Zuid-Holland	079-341 8238	rcpzuidwest@rivm.nl
RIVM-RCP Zuid	Zeeland / Noord-Brabant / Limburg	040-232 9111	rcpzuid@rivm.nl

Algemene informatie over het Rijksvaccinatieprogramma kunt u verkrijgen bij **RIVM/ Centrum Infectieziektebestrijding**, tel. 030-274 3433 of **RIVM/RCP Centraal**, tel. 030-274 8699.

Voor achtergrondinformatie over het Rijksvaccinatieprogramma verwijs ik u naar de Uitvoeringsregels RVP 2010, de VaccInformatiemap en naar de website www.rivm.nl/cib/rvp
Vragen over de VaccInformatiemap kunt u mailen aan rvpcommunicatie@rivm.nl

Exemplaren van deze richtlijnen kunt u downloaden van de website www.rivm.nl/cib/rvp of aanvragen bij het RIVM-RCP in uw werkgebied.

Dr. M.A.E. Conyn-van Spaendonck, arts-epidemioloog
RVP Programmamanagers Centrum
Infectieziektebestrijding

Bilthoven, december 2009

rijksvaccinatieprogramma

www.rvp.nl

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 a 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 ($\geq$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 op 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 en 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 than 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 acknowledges 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.
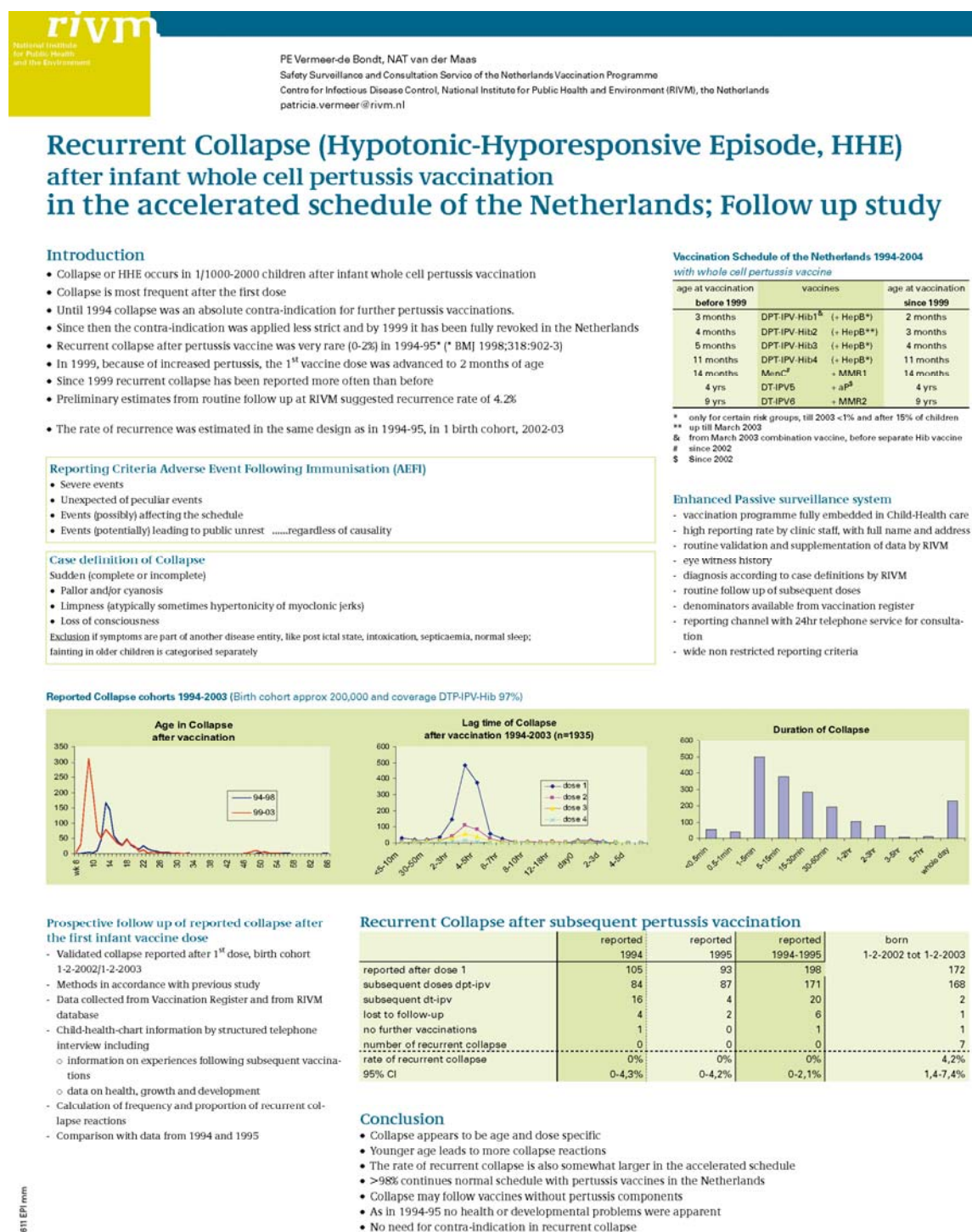The vaccination should always be in the differential diagnosis, nothing less but certainly nothing more!

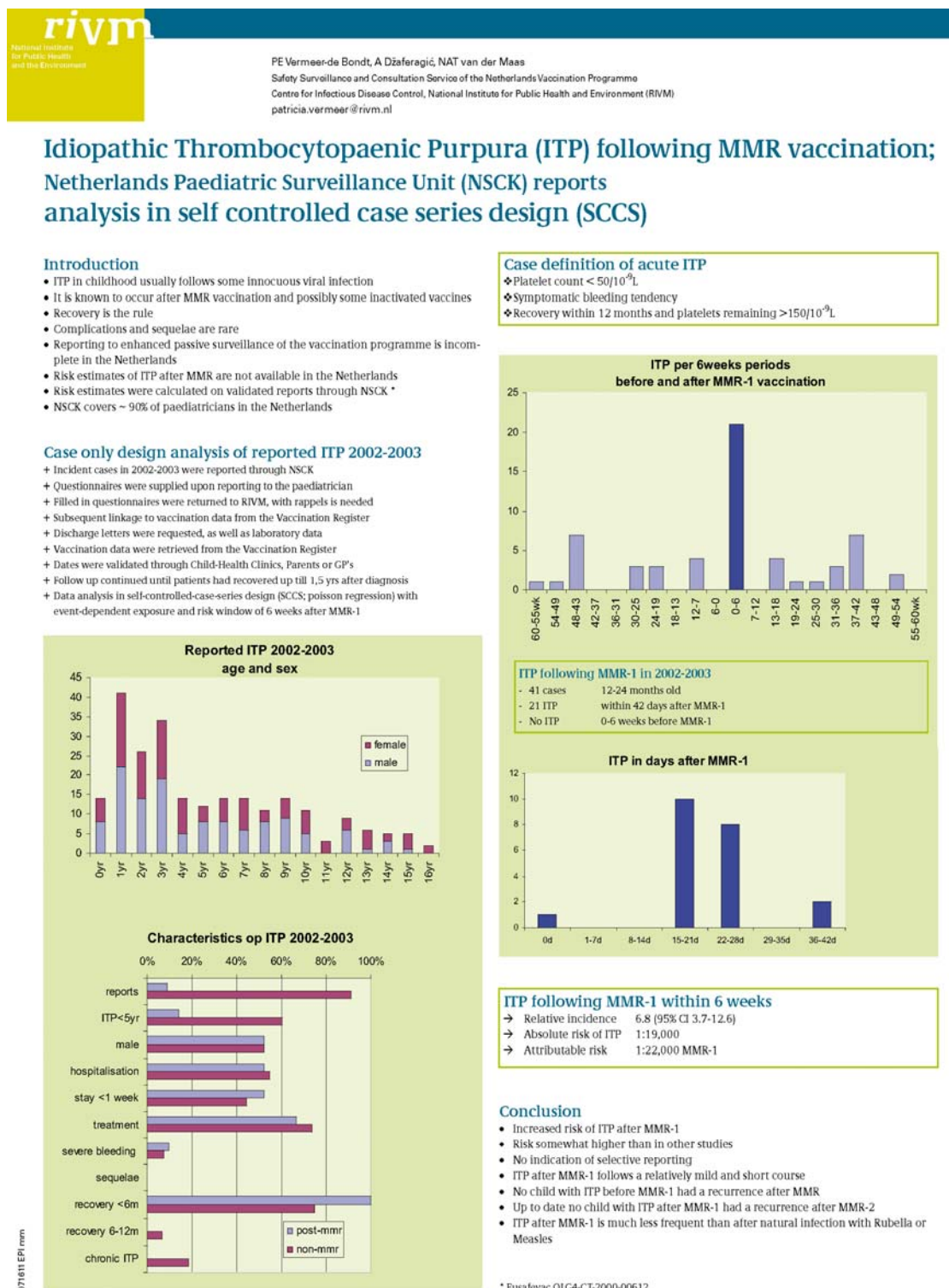   B.   Adverse events following MMR1 and MenC vaccinations

= 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 day12. Some children have very high fever ($\geq$40.5*C) with or without a rash.
Fever with or without rash is the most reported event in the passive system after MMR and MenC vaccination, covering around 40% of reports of which one third with very high fever ($\geq$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

Appendix 4B

rivm
National Institute
for Public Health
and the Environment

PE Vermeer-de Bondt, A Džaferagić, NAT van der Maas
Safety Surveillance and Consultation Service of the Netherlands Vaccination Programme
Centre for Infectious Disease Control, National Institute for Public Health and Environment (RIVM)
patricia.vermeer@rivm.nl

Idiopathic Thrombocytopaenic 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 innocuous viral infection
- It is known to occur after MMR vaccination and possibly some inactivated vaccines
- 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 validated reports through NSCK *
- NSCK covers ~ 90% of paediatricians in the Netherlands

Case only design analysis of reported ITP 2002-2003
+ Incident cases in 2002-2003 were reported through NSCK
+ Questionnaires were supplied upon reporting to the paediatrician
+ Filled in questionnaires were returned to RIVM, with rappels is needed
+ Subsequent linkage to vaccination data from the Vaccination Register
+ Discharge letters were requested, as well as laboratory data
+ Vaccination data were retrieved from the Vaccination Register
+ Dates were validated through Child-Health Clinics, Parents or GP's
+ Follow up continued until patients had recovered up till 1,5 yrs after diagnosis
+ Data analysis in self-controlled-case-series design (SCCS; poisson regression) with event-dependent exposure and risk window of 6 weeks after MMR-1

Case definition of acute ITP
❖ Platelet count < $50/10^{-9}$L
❖ Symptomatic bleeding tendency
❖ Recovery within 12 months and platelets remaining >$150/10^{-9}$L

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

Reported ITP 2002-2003 age and sex

ITP following MMR-1 in 2002-2003
- 41 cases   12-24 months old
- 21 ITP   within 42 days after MMR-1
- No ITP   0-6 weeks before MMR-1

ITP in days after MMR-1

Characteristics op ITP 2002-2003

ITP following MMR-1 within 6 weeks
→ Relative incidence   6.8 (95% CI 3.7-12.6)
→ Absolute risk of ITP   1:19,000
→ Attributable risk   1:22,000 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 no 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 Rubella or Measles

* Eusafevac QLG4-CT-2000-00612

071611 EPI mm

Appendix 4C

rivm
National Institute
for Public Health
and the Environment

Silke David, Patricia E Vermeer-de Bondt, Nicoline AT van der Maas
Safety Surveillance and Consultaion Service of the Netherlands Vaccination Programme
Centre for Infectious Disease Control, National Institute for Public Helath and Environment, the Netherlands
patricia.vermeer@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 passive safety surveillance system at RIVM
- Very adequate coverage in passive system for specific AE
- Supplemented systematic studies for tolerability, signal verification or hypothesis testing

Methods
- All infants vaccinated at participating child health clinics, with pertussis vaccines
- Questionnaire study December 2003-September 2007, no rappels
- Solicited adverse events, severe and uncommon
- Medical intervention paracetamol and or hospital visists
- OR and confidence intervals for proportions and their differences
- Data analysed with Access, Excel, Open Epi, Depid and Exactbin
- More detailed description of methods in Vaccine 2008: 26: 5883-7

Results
- Response rate 54%, wP =15069 and aP =13727
- Acknowledged Solicited AEFI for wP vs aP, = OR 2-7
- 51% male and 49 % female, no differences in reported AE or medication between sexes
- Paracetamol medication wP vs aP = OR 4.4 (95%CI 4.2-4.7)
- aP plus Pneu shows small increase in specific AE = OR 1.5 {95%CI 1.4-1.6}
  and some increase in therapeutic medication OR = 1.3 (95%CI 1.2-1.5),
  not only due to greater share of dose 4 in this subgroup.

Dutch infant vaccination schedule 2003-2007

Age	Vaccines^*
birth	HepB 0*
2 months	DTP-IPV-Hib 1 (+ HepB 1*) + Pneu 1$
3 months	DTP-IPV-Hib 2 (+ HepB 1*) + Pneu 2$
4 months	DTP-IPV-Hib 3 (+ HepB 1*) + Pneu 3$
11 months	DTP-IPV-Hib 4 (+ HepB 1*) + Pneu 4$

'wP vaccine (DPT-IPV-Hib) until January 2005 and two different aP vaccines since 2005
*HepB vaccine for defined risk groups (+15%)
$conjugated Pneu-vaccine for children born from 1-4-2006

Solicited Adverse Events in the questionnaire
1. prolonged crying > 1 hour, within 24 hours
2. fever > 39,5°C, within 24 hours
3. pallor, within 24 hours
4. fits or jerks, within 24 hours
5. use of paracetamol before or after vaccination
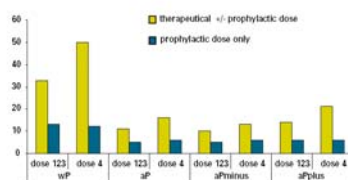
Figure 1 Medication, therapeutic or prophylactic only per vaccine dose; wP vs aP minus or plus Pneu
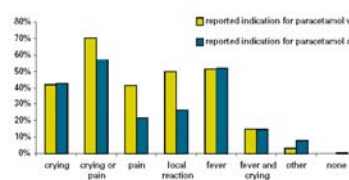
Figure 2 Reported indication for therapeutic paracetamol; wP versus aP
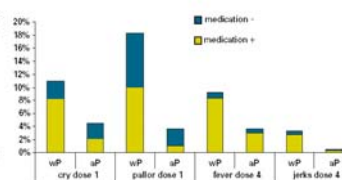
Figure 3 Medication per specific Adverse Event; wP versus aP

Table 1 Paracetamol per vaccine dose, wP vs aP, minus and plus Pneu; prophylactic, therapeutic or both;

	wP						aP						aP minus pneu				aP plus pneu			
	dose 123	%	dose 4	%	dose all	%	dose 123	%	dose 4	%	dose all	%	dose 123	%	dose 4	%	dose 123	%	dose 4	%
total doses	11490	46%	3560	61%	15069	49%	9384	17%	4342	22%	13727	18%	6451	15%	2768	19%	2933	19%	1546	27%
prophylactic	1498	13%	425	12%	1923	13%	493	5%	264	6%	757	6%	317	5%	169	6%	123	4%	86	6%
therapeutic	890	8%	509	14%	1399	9%	255	3%	233	5%	488	4%	150	2%	120	4%	107	4%	115	7%
both	2874	25%	1251	35%	4125	27%	801	9%	453	10%	1254	9%	487	8%	243	9%	314	11%	210	14%

Conclusion
- Decreased use of paracetamol since the transition to acellular pertussis vaccinations in infancy
- Since introduction of simultaneous Pneu vaccine some increase in paracetamol use
- No differences in solicited adverse events between male and female, nor in paracetamol use
- Estimated number of paracetamol doses for wP schedule at least 600,000 per year and at least 220,000 for aP schedule
- Trade off between (perceived) tolerability of infant vaccinations with subsequent coverage and side effects of paracetamol; what is the balance?
- Paracetamol may mask coincidental events following vaccinations, with possible delay in timely recognition and management
- Further education of parents warranted, especially with regard of the management of fever, eg cool clothing and wet sponging?
- Improvement in technical procedures of vaccine administration in order to diminish local reactions and pain

090663 KH

Appendix 4D

Appendix 4E

National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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 4-years-old-booster DT-IPV since cohort 1998
- Infant schedule (4 doses) shifted from whole-cell to acellular pertussis combination-vaccines in 2005
- In 2008 reports of local reactions with / without fever suddenly increased
- Types and brands of vaccines have differed, both for infants and for boosters
- Our interest is their effect on risk of adverse events (AE) after the 4y-booster

Methods

- Reports (n=1809) over 1995-2010 for 1991-2006 cohorts were categorised using the standardised criteria for diagnosis (annual AE reports, www.rivm.nl)
- Coverage-denominators (date, age, sex, vaccine dose, vaccine type) were available from the National Vaccination Register

National Vaccination Programme in 2010

age	Vaccines*	
2 months	DTP-IPV-Hib(-hepB)	Pneu
3 months	DTP-IPV-Hib(-hepB)	Pneu
4 months	DTP-IPV-Hib(-hepB)	Pneu
11 months	DTP-IPV-Hib(-hepB)	Pneu
14 months	MMR	MenC
4 years	DTP-IPV	
9 years	DT-IPV	MMR
13 years	HPV 3 doses	Girls only

* hepB only for risk groups (15%)

Results

- Reports numbered about 25 annually for cohorts 1991-1997, most frequently fainting, local reactions and fever, equal to 13 reports per 100,000 vaccinees
- After introduction of pertussis boosters at 4 years of age in 2002 (cohort 1998) reports increased to 75 on average, i.e. 39/100,000 vaccinees
- In 2008 a sharp increase in reports occurred with 580 reports in 2009 (325/100,000 vaccinees)
- The increase in reports was mainly due to local reactions, often severe/extreme and some increase in fever
- This increase was associated with acellular pertussis in the infant schedule
- Originally reports concerned those who received acellular vaccine by parental choice ahead of the universal transition from whole cell to acellular pertussis vaccine
- Reporting rate decreased somewhat again in 2010, possibly because of different vaccines in the infant schedule and perhaps less complete reporting
- For other vaccines in the vaccination programme the reporting rates have not shown similar increases
- The local reactions have been treated with antibiotics more often than warranted
- Misdiagnosis of anaphylactic reaction of extreme local reactions has caused apprehension in vaccinees and parents with subsequent abandonment of any vaccination

Vaccination Schedule and Vaccines for infants and 4 year-olds over the years

cohort	1991-1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Infant 4 doses	whole cell vaccine DT-wP-IPV-Hib (+hepB)								acellular vaccine DTaP-IPV-Hib(+hepB)	
vaccine	RIVM-DKTP-Hib								Infanrix-IPV-Hib	Pediacel (or Infan-rixHexa)
4 years booster	No pertus-sis DT-IPV	+acellular vaccine DT-IPV +aP			acellular combined vaccine DTaP-IPV					
vaccine	RIVM-DTP	Single aP added RIVM/GSK			Triaxis-polio	Infanrix-IPV				

aP=acellular pertussis vaccine
wP=whole cell pertussis vaccine

Figure 1: Reported AE following booster vaccination at 4 years of age per 100,000 vaccinees
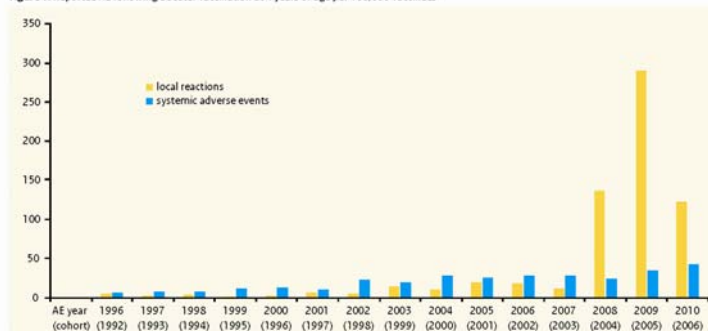
Conclusions

- The increase in reported severe or extreme local reactions after booster with DTaP-IPV at 4 years of age was related to the transition to acellular vaccines for infants.
- Reporting rates have increased from approximately 1/7500 in the years up till 2001 and 1/2500 in 2002-2007 to 1/300 in 2008
- Some indication was found that the occurrence of reported local reactions may be influenced by specific acellular vaccines in the infant and 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 so far unclear pathogenesis
- Attention should be paid to proper management of local reactions.
- Unnecessary treatment of local reactions with antibiotics or faulty attribution to acute allergic reaction must be avoided, in order to reduce abandonment of any further vaccination

Authors: Patricia E. Vermeer-de Bondt, Bregje Oostvogels, Tieke A. J. Phaff, Nicoline A.T. van der Maas
patricia.vermeer@rivm.nl

Centre for Infectious Disease Control, National Institute for Public Health and Environment

**P.E. Vermeer-de Bondt | N. Moorer-Lanser | T.A.J. Phaff |
B. Oostvogels | C. Wesselo | N.A.T. van der Maas**

003331