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

# The National Immunisation Programme in the Netherlands

*Developments in 2010*

Report 210021013/2010

H.G.A.M. van der Avoort et al.

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RIVM Report 210021013/2010

# Colophon



Editors:
N.A.T. van der Maas
M. Hoogeveen
H.E. de Melker

Report prepared by:
H.G.A.M. van der Avoort, G.A.M. Berbers, R.S. van Binnendijk, H. Boogaards, H.J. Boot, G.P.J.M. van den Dobbelsteen, M.C.W. Feltkamp, I.H.M. Friesema, S.C. de Greeff, S.J.M. Hahné, J.M. Kemmeren, F.R.M. van der Klis, T. van 't Klooster, F. Koedijk, E.A. van Lier, N.A.T. van der Maas, H.E. de Melker, M. Mollers, F.R. Mooi, D. Nootermans, W. van Pelt, F. Reubsaet, M. van der Sande, L.M. Schouls, L. Verhoef, R. Vriend, C.C.H. Wielders

Contact:
H.E. de Melker
Centre for Infectious Disease Control
hester.de.melker@rivm.nl

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# Abstract

**The National Immunisation Programme in the Netherlands**
Developments in 2010

This report presents the developments of the NIP in 2010, supported by updated surveillance data of current and potential target diseases.

High vaccination coverage for many years has resulted in low incidences for most target diseases in 2010 (diphtheria, tetanus, polio, Hib, measles, rubella, meningococcal group C disease). As a result of strong reduction of vaccine types, pneumococcal disease is reduced among the age groups targeted for vaccination. However the indications of herd immunity are counteracted by increased incidence for non-vaccine types. For pertussis, a further increase in incidence among adolescents and adults is observed. Cocooning might be an effective way to reduce the incidence among infants too young to be vaccinated. The recent mumps outbreak in vaccinated adolescents raised concern about vaccine effectiveness. Studies have been initiated. HPV vaccination introduced in the NIP in 2010 resulted in an uptake of the first dose of 56% among 12-year-olds. Studies to evaluate the efficacy of HPV vaccination are ongoing.
In general, the HPV vaccination was experienced as painful among girls aged 13-16 years but adverse events were mostly mild and all transient.

Incidences of meningococcal group B disease and hepatitis A are decreasing, rotavirus incidence appears to be rising and no changes have been observed with regard to VZV epidemiology. These data need to be considered in any decision-making on these potential new target diseases. In 2011 the NIP will be adapted: i.e., a 10-valent conjugated pneumococcal vaccine will replace the currently used 7-valent vaccine and universal HBV vaccination for infants will be implemented.

Though continuing surveillance is needed, we can conclude that the Dutch NIP is effective and safe.

Key words:
National Immunisation Programme, rotavirus, varicella zoster, meningococcal B disease, hepatitis A

# Rapport in het kort

**Het Rijksvaccinatieprogramma in Nederland**
Ontwikkelingen in 2010

Dit rapport geeft een overzicht van het voorkomen van verwekkers van ziekten uit het Rijksvaccinatieprogramma (RVP), een overzicht van veranderingen in de verwekkers, de gebruikte vaccins en bijwerkingen na vaccinatie in 2010. Hetzelfde geldt voor ontwikkelingen over nieuwe vaccins, die in de toekomst eventueel in het RVP worden opgenomen.

In 2010 is vaccinatie tegen baarmoederhalskanker toegevoegd aan het Rijksvaccinatieprogramma. In 2011 zal worden overgegaan op een pneumokokkenvaccin dat bescherming biedt tegen tien typen in plaats van het nu gebruikte vaccin met zeven typen. Ook vaccinatie tegen een Hepatitis B infectie wordt voor het eind van 2011 geïntroduceerd.

Door een voortdurende hoge vaccinatiegraad is ook in 2009 en 2010 het aantal gevallen van de meeste ziekten uit het RVP laag.

Voor kinkhoest is het aantal meldingen van adolescenten en volwassenen in 2010 verder toegenomen. ”Cocooning’ (het vaccineren van ouders van pasgeboren baby’s) zou een goede manier kunnen zijn om ernstige kinkhoest infecties bij zuigelingen te voorkomen. Een recente bof uitbraak onder gevaccineerde jong volwassenen is aanleiding geweest voor het opzetten van enkele onderzoeken naar de effectiviteit van het vaccin. Studies om de effectiviteit van HPV-vaccinatie te onderzoeken lopen. Gegevens over mogelijke bijwerkingen na HPV vaccinatie laten laten zien dat meisjes de vaccinatie als pijnvol ervaren, maar dat de bijwerkingen grotendeels mild en van voorbijgaande aard zijn.

Van de ziekten die mogelijk in de toekomst onder het RVP gaan vallen, komen infecties door Meningokokken groep B en Hepatitis A virus minder voor. Rotavirus infecties die leiden tot gastro-enteritis nemen toe. Er zijn geen grote veranderingen waargenomen in de frequentie en de ernst van het ziekteverloop van waterpokken en gordelroos. Resultaten van meederde studies over deze laatste twee ziektes zullen in 2011 gepresenteerd worden.

Dankzij continue surveillance en controle, kunnen wij concluderen dat het RVP momenteel effectief en veilig is.

Trefwoorden:
Rijksvaccinatieprogramma, rotavirus, varicella zoster, meningokokken B, hepatitis A

# Preface

This report gives an overview of the developments in 2010 for the diseases included in the current National Immunisation Programme (NIP): diphtheria, pertussis, tetanus, poliomyelitis, *Haemophilus influenzae* serotype b (Hib) disease, mumps, measles, rubella, meningococcal serogroup C disease, hepatitis B (risk groups only), pneumococcal disease and human papillomavirus (HPV) infection.
Furthermore, surveillance data with regard to potential new target diseases, for which a vaccine is available, are described: rotavirus infection, varicella zoster virus (VZV) infection and hepatitis A infection. In addition, meningococcal serogroup B disease is included in this report, since a new vaccine has been developed and registration will be applied for in the near future.

The report is structured as follows. Chapter 1 describes surveillance methods, generally used to monitor the NIP. Recent results on vaccination coverage of the NIP are discussed in chapter 2. Chapter 3 focuses on current target diseases of the NIP. For each disease, key points mark the most prominent findings, followed by an update of information on epidemiology, pathogen and adverse events following immunisation (AEFI). Results of ongoing studies are described, together with the planning of future studies. If applicable, recent and planned changes in NIP are mentioned. Chapter 4 describes new target diseases, with which the NIP could be extended in the future. In Appendix 1 mortality and morbidity figures from 1997 onwards from various data sources per disease are published.

This report informs the Health Council and Ministry of Health, Welfare and Sport (VWS) on developments with respect to vaccine preventable diseases.

# Contents

# List of abbreviations

| | |
|---|---|
| ACA | Acute Cerebellar Ataxia |
| ACIP | Advisory Committee on Immunisation Practices |
| AE | Adverse Event |
| AEFI | Adverse Events Following Immunisation |
| AFP | Acute Flaccid Paralysis |
| aP | acellular Pertussis |
| CI | Confidence Interval |
| CIb | Centre for Infectious Disease Control, the Netherlands |
| CIN | cervical intraepithelial neoplasia |
| c-VDPV | circulating Vaccine-Derived Polio viruses |
| DTP | Combination of Diphtheria, Tetanus, and Pertussis vaccines |
| ECDC | European Centre for Disease Control and Prevention |
| ELISA | Enzyme-Linked ImmunoSorbent Assay |
| FHA | Filamentous Haemagglutinin |
| GP | General Practitioner |
| GSK | Glaxo Smith Kline |
| HBsAg | Hepatitis B surface Antigen |
| HBV | Hepatitis B Virus |
| Hib | *Haemophilus influenzae* type b |
| HPV | Human papillomavirus |
| hrHPV | high-risk Human papillomavirus |
| ICD | International Classification of Diseases |
| ICER | Incremental Cost Effectiveness Ratio |
| IPCI | Integrated Primary Care Information |
| IPD | Invasive Pneumococcal Disease |
| IPV | Inactivated Polio Vaccine |
| iVDPV | VDPVs that can be attributed to an immuno-compromised person |
| Men C | Meningococcal C |
| MHS | Municipal Health Service (GGD) |
| MMR | Combination of Measles, Mumps, and Rubella vaccines |
| MMRV | Combination of Measles, Mumps, Rubella, and Varicella vaccines |
| mOPV | monovalent Oral Polio Vaccine |
| MS | Multiple Sclerosis |
| MSM | Men having Sex with Men |
| NID | National Immunisation Day |
| NIP | National Immunisation Programme |
| NIVEL | Netherlands Institute for Health Services Research |
| NPL | National Polio Laboratory |
| NPG | National Influenza Prevention Programme |
| NRBM | Netherlands Reference laboratory for Bacterial Meningitis |
| NVI | Netherlands Vaccine Institute |
| PCR | Polymerase Chain Reaction |
| PCV | Pneumococcal Conjugate Vaccine |
| PIENTER | Assessing Immunisation Effect To Evaluate the NIP |
| Pneumo | Pneumococcal vaccination |
| Prn | Pertactin |
| QALY | Quality Adjusted Life Years |
| OPV | Oral Polio Vaccine |
| RIVM | National Institute for Public Health and the Environment, the Netherlands |

| | |
|---|---|
| SAE | Severe Adverse Event |
| SP-MSD | Sanofi Pasteur MSD |
| STI | Sexually Transmitted Infections |
| tOPV | trivalent Oral Polio Vaccine |
| VDPV | Vaccine-Derived Polio Virus |
| VE | Vaccine Efficacy |
| VZV | Varicella Zoster Virus |
| VWS | Ministry of Health, Welfare and Sport |
| WHO | World Health Organisation |
| WPV | Wild Polio virus |

# Summary

This report presents current vaccination schedules, surveillance data and scientific developments in the Netherlands for vaccine preventable diseases that are included in the NIP (diphtheria, pertussis, tetanus, poliomyelitis, Hib, measles, mumps, rubella, meningococcal serogroup C disease, hepatitis B, pneumococcal disease and HPV) and new potential target diseases for which a vaccine is available (rotavirus, VZV and hepatitis A) or might become available in the near future (Meningococcal serogroup B disease).

Through the NIP, children in the Netherlands are offered their first vaccinations, DTaP-IPV-Hib and pneumococcal disease, at the age of 2, 3, 4 and 11 months. Subsequently, vaccines against MMR and meningococcal C disease are administered simultaneously at 14 months of age. DTap-IPV is then given at 4 years and DT-IPV and MMR at 9 years old. New in 2010 is an additional round of 3 vaccinations for 12-year-old girls against HPV.

For children of whom at least one parent was born in a HBV endemic country or of whom the mother tested positive for HBaAg, a DTaP-HBV-IPV-Hib vaccine will be offered instead of the DTaP-IPV-Hib vaccine. In addition, children of HBsAg positively tested mothers are provided a HBV vaccination within 48 hours after birth.

Average participation for NIP vaccinations was above the WHO lower limit of 90% for 2010. The lower limit of 95% for MMR vaccination was reached for the first MMR vaccination round (14 months), but not for the second round (9 years). An outbreak of measles is therefore possible. Participation for HBV vaccination among children has further increased to 94.2%. Attention is still needed for children of mothers that are HBV carriers, since HBV infection at a young age results in a higher risk of becoming a carrier and of contracting liver disorders.

**Diphtheria**

In 2010 no cases of diphtheria were reported in the Netherlands. Test results on two isolates, which were sent to RIVM, were comparable with earlier years.

**Pertussis**

The circulation of pertussis among adolescents and adults more than doubled in the past decade. However, the highest morbidity and mortality due to pertussis is found in 0-6-month-old infants, who are too young to be fully vaccinated. A study on the direct costs of pertussis carried out by the RIVM suggests that cocooning vaccination will be more attractive from an economical point of view than repetitive adolescent and adult vaccination.

Higher frequency of (severe) local reactions after the booster vaccination with a combined diphtheria, tetanus, and acellular pertussis vaccine (dTaP) at 4 years of age was observed for those cohorts that received acellular pertussis vaccine in the primary series. The spacing between the primary series (2, 3, 4, and 11 months) and the booster at 3-4 years was based on the WCV. With the introduction of a more effective ACV, the booster could be delayed until the age of 5-6 years. This will increase the duration of protection and possible also reduce side

effects. Furthermore, vaccines with reduced antigen content may decrease the reactogenicity of booster vaccinations.
The emergence of more virulent strains and escape variants, which do not produce pertussis toxin and pertactin, underline the need to improve pertussis vaccines. Strains, which do not produce pertactin, have now been isolated in both France and Japan. Furthermore, in France, B. parapertussis strains devoid of pertactin have also been isolated. As yet, strains devoid of proteins used in pertussis vaccines have not been found in the Netherlands.

**Tetanus**

Tetanus is again notifiable since 2009. In 2010, 2 cases of tetanus were notified, a 77-year-old woman and a 71-year-old man. Both were unvaccinated and survived after hospitalisation.
Immunity against tetanus in the Dutch population is adequate. However, a recent sero-epidemiological study identified tetanus in individuals born before the introduction of routine vaccination, first-generation migrants from non-western countries born before 1984 and protestants living in the Dutch Bible belt.

**Poliomyelitis**

No cases of polio were reported in the Netherlands in 2010. However the polio-free status of the European Region of the WHO (declared on June 21st, 2002) is at stake, due to an epidemic that originated in Tajikistan and spread to Kazakhstan, Turkmenistan, the Russian Federation and most likely also to Uzbekistan.
The notification of cases in the Caucasus region of the Russian Federation is of importance for the Netherlands, as this region neighbours Turkey, the origin of the viruses that caused the last 2 poliomyelitis outbreaks in the Netherlands (1978 and 1992/3).
The total number of cases in the four traditional endemic countries (Nigeria, Northern India, Afghanistan and Pakistan) has dropped dramatically in the last two years and is much lower than the number of cases due to importations from these countries.
The definition of vaccine derived polioviruses (VDPVs) has been adapted. Any type 2 poliovirus with 6 or more changes from Sabin 2 will be considered a "vaccine-derived poliovirus" of programmatic importance, regardless of its source; the definition of type 1 and type 3 VDPVs remains unchanged (≥ 10 changes in VP1).

**Hib**

There have been no significant changes in number or nature of the invasive disease cases caused by Hib in 2010. No changes in the composition and characteristics of the Hib strains causing invasive disease have been observed.

**Mumps**

An outbreak that started among vaccinated adolescent students in 2009 continued in 2010. Up to week 44 in 2010, 391 mumps cases were reported, including 7 hospitalisations.

The outbreak raised concern on vaccine effectiveness, which may be affected by waning immunity and therefore studies have been initialised.

**Measles**

In 2010, up to week 44, 11 cases have been notified. Incidence of measles in 2009 was 0.9/1,000,000 population, which is below the WHO elimination target.

**Rubella**

Incidence of rubella was 0.05/100,000 in 2009 and occurred mainly among persons with a critical attitude towards vaccination. A genotype could not be determined for the reported cases. In 2010 no cases were notified.

**Meningococcal serogroup C disease**

Since the introduction of the conjugated MenC vaccine, the incidence of serogroup C disease has strongly decreased. In 2009, 9 cases were notified with invasive serogroup C disease. However, no cases in previously vaccinated persons have been reported since the start of the vaccination in 2002.

**Hepatitis B**

Notification data suggest the decrease in incidence of acute hepatitis B since 2003 was sustained in 2009. Infections acquired through heterosexual contact outnumbered those through male homosexual contact.

In 2011, universal infant vaccination against HBV will be introduced.

**Pneumococcal disease**

Introduction of vaccination against pneumococcal disease has led to a considerable reduction in the number of cases with invasive pneumococcal disease (IPD) caused by vaccine types in both vaccinated cohorts and persons not eligible for vaccination. However, at the same time, an increase in non-vaccine serotypes is seen.

**HPV**

In 2010, vaccination coverage for the first and second dose in the first NIP cohort, i.e., girls born in 1997, was 56% and 53%, respectively. The coverage among girls of the catch-up campaign increased to 47% in 2010, since they were offered a second opportunity for vaccination. A recent modelling study observed that cost-effectiveness of HPV vaccination in the Netherlands is not negatively affected by the unexpectedly low vaccination uptake, especially if herd immunity is taken into account.

The report rate for spontaneously reported adverse events after the HPV catch-up campaign in 2009 was 11.6 per 10,000 administered doses. No Severe Adverse Events (SAE) with assessed causality were reported. The report rate of presyncope and syncope after the HPV catch-up campaign in 2009 was 16.8 per 10,000 administered doses. Local reactions, such as pain at the

injection site and reduced use of the arm, were reported in ~85% of the girls after the HPV catch-up campaign. Systemic events, such as myalgia, fatigue and headache were reported in ~83% of the girls. HPV seropositivity increases significantly with age, starting at the age of 16 years. A former diagnosis of a sexually transmitted disease is significantly associated with HPV seropositivity.

VE against cervical intraepithelial neoplasia 2+ (CIN2+), associated with HPV16/18 is high (above 90% after approximately three years of follow-up). The vaccine also protects against CIN2+ caused by non-vaccine oncogenic HPV types (cross-protection). It is important to be aware of possible changes in HPV genotype distribution and changes in antigenicity of the circulating HPV16/18 genotypes.

**Rotavirus**

The incidence of rotavirus associated gastroenteritis appears to be rising.

Rotavirus is the most important cause in case of hospitalisation due to gastro-enteritis in children aged younger than 5 years. In a recent Dutch study, one in five adults hospitalised with gastroenteritis had a rotavirus infection. In the Netherlands, serotype G1[P8] is the most common type.

Several countries show a marked reduction of hospitalisation and emergency department visits for gastroenteritis after the implementation of vaccination against rotavirus. Furthermore, herd immunity is reported. In Belgium, an increase in the non-vaccine serotype G2 has been seen since the introduction of rotavirus vaccination.

**VZV infection**

While the incidence of hospitalised varicella cases in the Netherlands is lower compared with other (European) countries, the severity of varicella disease among hospitalised patients seems to be similar to that of other countries.

No striking changes occurred in the VZV epidemiology in the Netherlands in 2009: the lower reported incidence of general practitioner consultations due to varicella in the Continuous Morbidity Registration is related to changes in the reporting system.

The results for various studies (GP consultations, seroprevalence, cost-effectiveness and mathematical modelling) are expected in 2011 and will be input in the consideration of the Health Council on universal varicella vaccination.

**Hepatitis A**

The long-term decreasing trend of infections with Hepatitis A virus since the early nineties continues (269 cases in 2008, 178 cases in 2009). Almost half of all cases is travel related (42%).

The susceptible population in the Netherlands is increasing in age, which is a point of concern that should be the future focus for public health action. Furthermore, they can develop clinically serious symptoms after infection and are increasingly at risk of exposure through viruses imported though foods or by travellers.

**Meningococcal serogroup B disease**

MenB is decreasing, though there is no vaccine against infections with serogroup B meningococci.

**Conclusion**

Though continuing surveillance is needed, we can conclude that the Dutch NIP is effective and safe.

# 1 Surveillance methodology

## 1.1 Introduction

Vaccination of a large part of the population in the Netherlands against diphtheria, tetanus and pertussis (DTP) was introduced in 1952. The National Immunisation Programme (NIP) was started in 1957, offering DTP and inactivated polio vaccination (IPV) in a programmatic approach to all children born from 1945 onwards. Nowadays, vaccination against measles, mumps, rubella (MMR), *Haemophilus influenzae* type b (Hib), meningococcal C disease (Men C), pneumococcal disease, human papillomavirus (HPV) and hepatitis B (HBV; for high-risk groups only) is included in the programme. The vaccines that are currently administered and the age of administration are specified in Table 1. Vaccinations within the NIP in the Netherlands are administered to the target population free of charge and on a voluntary basis. In addition to diseases included in the NIP, influenza vaccination is offered through the National Influenza Prevention Programme (NPG) to individuals aged 60 years and over and individuals otherwise considered at increased risk of morbidity and mortality following an influenza infection in the Dutch population. Furthermore, vaccination against tuberculosis is offered to children of immigrants from high prevalence countries. For developments on influenza and tuberculosis we refer to reports of the Health Council and the KNCV Tuberculosis Foundation.[1-3] Besides HBV included in the NIP, for children of whom at least one parent was born in a middle or high HBV endemic country or the mother is HBV carrier, a vaccination programme targeting groups at risk for HBV due to sexual behaviour or profession is in place in the Netherlands.

In 2009, vaccination against Influenza A (H1N1) was offered to all people eligible for routine seasonal flu vaccination, all pregnant women in the second and third trimester, children between 6 months and 5 years of age and household members of infants younger than 6 months. For children, routine NIP vaccines were postponed until January 2010, in order to avoid possible interference with the H1N1 vaccine.

**Table 1 Vaccination schedule of the NIP from 2006 to 2009***

| Age | Injection 1 | Injection 1 (risk groups only)[a] | Injection 2 |
|---|---|---|---|
| At birth (<48 hours) | | HBV [b] | |
| 2 months | DTaP-IPV/Hib | DTaP-HBV-IPV/Hib | Pneumo |
| 3 months | DTaP-IPV/Hib | DTaP-HBV-IPV/Hib | Pneumo |
| 4 months | DTaP-IPV/Hib | DTaP-HBV-IPV/Hib | Pneumo |
| 11 months | DTaP-IPV/Hib | DTaP-HBV-IPV/Hib | Pneumo |
| 14 months | MMR | MMR | Men C |
| 4 years | DTaP-IPV | DTaP-IPV | |
| 9 years | DT-IPV | DT-IPV | MMR |
| 12 years | HPV[c] | | |

[a] Only for children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for Hepatitis B surface Antigen (HBsAg).

[b] Only for children of whom the mother tested positive for HBsAg.

[c] Only for girls; three doses at 0 days, 1 month, 6 months.

Source: http://www.rivm.nl/rvp/rijks_vp/vac_schema/

The ultimate goal of the NIP is the eradication of all vaccine preventable diseases targeted by the programme, although this goal is unattainable at least for tetanus, due to the non-human reservoir of this disease. A next step will be to reach the target, set by WHO-Euro, to eliminate measles and rubella by 2015 and to the global goal of polio eradication. The Centre for Infectious Disease Control (Cib), part of the National Institute for Public Health and the Environment (RIVM), is responsible for managing and monitoring the NIP. For monitoring, a constant input of surveillance data is essential. Surveillance is defined as the continuous and systematic gathering, analysis and interpretation of data. It is a very important instrument to identify risk-groups, trace disease sources and certify elimination and eradication. Results of surveillance offer information to the Health Council, the Ministry of Health, Welfare and Sports (VWS) and other professionals to decide whether or not actions are needed to improve the NIP. Surveillance of the NIP consists of five pillars, described in the following sections.

## 1.2 Disease surveillance

For all target diseases of the NIP, the impact of the programme can be monitored through mortality, morbidity and laboratory data related to the specific diseases.

### *1.2.1 Mortality data*

The Central Bureau of Statistics (CBS) registers mortality data from death certificates on a statutory basis. The registration specifies whether it concerned a natural death, a non-natural

death or a stillborn child. In case of natural death, the physician should report the following data:

1. Illness or disease that has led to the cause of death (primary cause).
2. a. Complication, directly related to the primary cause, which has led to death (secondary cause).
   b. Additional diseases and specifics still present at the moment of death, which have contributed to the death (secondary causes).

CBS codes causes of death according to the International Classification of Diseases (ICD). This classification is adjusted every 10 years or so, which has to be taken into account when following mortality trends.

### *1.2.2 Morbidity data*

#### 1.2.2.1 Notifications

Notifications by law are an important surveillance source for diseases included in the NIP. Notification of infectious diseases started in the Netherlands in 1865. Since then, several changes in notification were enforced. Not all diseases targeted by the NIP were notifiable during the entire period. See Table 2 for more information.[4]

**Table 2: periods of notification for vaccine preventable diseases, included in the National Immunisation Programme**

| **Disease** | **Periods of notification by legislation** |
|---|---|
| Diphtheria | from 1872 onwards |
| Pertussis | from 1975 onwards |
| Tetanus | 1950-1999, from December 2008 onwards |
| Poliomyelitis | from 1923 onwards |
| Invasive *Haemophilus influenzae* type b | from December 2008 onwards |
| Hepatitis B disease | from 1950 onwards |
| Invasive pneumococcal disease[a] | from December 2008 onwards |
| Mumps | 1975-1999, from December 2008 onwards |
| Measles | 1872-1899, from 1975 onwards |
| Rubella | from 1950 onwards |
| Invasive meningococcal disease | from 1905 onwards |

[a] = for infants only

In December 2008, a new law was set up which led to notification of all NIP targeted diseases as physicians, laboratories and heads of institutions now had to report 42 notifiable infectious diseases, instead of 36, to the Public Health Services (Wet Publieke Gezondheid).

There are four categories of notifiable diseases. Diseases in category "A" have to be reported directly by telephone following a laboratory confirmed diagnosis. Diseases in the categories "B1", "B2" and "C" must be reported within 24 hours or one working day after laboratory confirmation. However, for several diseases there is underreporting and delay in reporting.[5] For instance, a seroprevalence study on pertussis revealed that about 9% of people over 9 years of

age had a recent pertussis infection, often in a mitigated form, not resulting in consultation with a GP.[6] In each of the latter three categories, different intervention measures can be enforced to prevent spreading of the disease.

Poliomyelitis is included in category A, diphtheria in category B1. Pertussis, measles, rubella and hepatitis A and B are category B2 diseases. The fourth category, C, includes mumps, tetanus, meningococcal disease, invasive pneumococcal disease and invasive Hib.

#### 1.2.2.2 Hospital admissions

The National Medical Registration (LMR), managed by research institute Prismant, collects acquittal diagnoses of all patients that are admitted to a hospital. Outpatient diagnoses are not registered. Diseases, including all NIP target diseases, are coded as the main or side diagnosis according to the ICD-9 coding. The coverage of this registration was about 99% until mid-2005. Thereafter, coverage fluctuates around 90%, due to changes in funding. Hospital admission data are also sensitive for underreporting, as shown by de Greeff et al. in a paper on meningococcal disease incidence.[7]

Data on mortality and hospitalisation are not always reliable, particularly for diseases that occur sporadically. For tetanus, tetani cases are sometimes incorrectly registered as tetanus[8] and for poliomyelitis, cases of post-poliomyelitis syndrome are sometimes classified as acute poliomyelitis, while these occurred many years ago. Furthermore, sometimes cases of acute flaccid paralysis (AFP) with other causes are inadvertently registered as cases of acute poliomyelitis.[8] Thus, for poliomyelitis and tetanus, notifications are a reliable source of surveillance

### *1.2.3 Laboratory data*

Laboratory diagnostics are very important in monitoring infectious diseases and the effectiveness of vaccination; about 75% of all infectious diseases can only be diagnosed by laboratory tests.[9] However, limited information on patients is registered and often laboratory confirmation is not sought for self-limiting vaccine preventable diseases. Below, the different laboratory surveillance systems for diseases targeted by the NIP are outlined.

#### 1.2.3.1 Netherlands Reference Laboratory Bacterial Meningitis

The Netherlands Reference Laboratory Bacterial Meningitis (NRBM) is a collaboration between RIVM and the Academic Medical Centre of Amsterdam (AMC). Microbiological laboratories throughout the Netherlands send, on a voluntary basis, isolates from blood and cerebrospinal fluid (CSF) of patients with invasive bacterial disease to the NRBM for further typing. For CSF isolates, the coverage is almost complete. Nine sentinel laboratories throughout the country are asked to send isolates from all their patients with IPD and, based on the number of CSF isolates, their overall coverage is around 25%.

Positive results of pneumococcal, meningococcal and haemophilus diagnostics and typing are relevant for the NIP surveillance.

#### 1.2.3.2 Virological laboratories

Virological laboratories, joined in the Dutch Working Group for Clinical Virology, weekly send positive results of virological diagnostics to RIVM. Approximately 25 laboratories send in information regularly. Aggregated results are shown on the RIVM website. It is important to keep in mind that the presence of the virus does not automatically implicate disease. Information on the number of tests done is not collected.

## 1.3 Molecular surveillance of the pathogen

The monitoring of strain variations due to differences in phenotype and/or genotype is important to gather information on the emergence of (sub)types, which may be more virulent or less effectively controlled by vaccination. It is also a useful tool to improve insight into transmission dynamics.

## 1.4 Immunosurveillance

Monitoring the seroprevalence of all NIP target diseases is a way to gather age and sex specific information on immunity against these diseases, acquired through natural infection or vaccination. To this end, a random selection of all people living in the Netherlands is periodically asked to donate a blood sample and fill in a questionnaire (PIENTER survey). This survey was performed in 1995-1996 and 2006-2007 among 20,000 Dutch inhabitants. Oversampling of people living in regions with low vaccine coverage or of immigrants is done to gain more insight into differences in immunity among specific groups.

## 1.5 Vaccination coverage

Vaccination coverage data can be used to gain insight in the effectiveness of the NIP. Furthermore, this information can identify risk groups with low vaccine coverage, who are more susceptible to one of the NIP target diseases. In the Netherlands, all vaccinations, administered within the framework of the NIP are registered in a central web-based database on the individual level.

## 1.6 Surveillance of adverse events following vaccination

Since 1962, RIVM is responsible for the safety surveillance of the NIP. An enhanced spontaneous reporting system for Adverse Events following Immunisation (AEFI) is combined with a telephone service for consultation and advice on schedules, contraindications, precautions, adverse events and other vaccination related problems. All incoming reports are accepted, irrespective of causal relation. After thorough validation and supplementation of the information, a (working) diagnosis is made and causality is assessed, based on international criteria (Table 3).

**Table 3 Criteria for causality categorisation of AEFI**

| Criteria | Causality 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 biological plausibility and fitting interval without indication of other causes |
| 3-Possible | involvement of the vaccine is conceivable because of the interval and the biological plausibility, but other cause are plausible/possible as well |
| 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 |

AEFI with certain, probable or possible causal relation to vaccinations are considered adverse reactions (AR), also called 'true side-effects'. AEFI with an improbable causality are defined as coincidental events or chance occurrences.

Aggregated analysis of all reported AEFI is published annually by RIVM. Due to a high reporting rate and the consistent methodology, trend analysis is possible.[10] This spontaneous reporting system is supplemented with other, more systematic ways of safety surveillance, for instance, questionnaire surveys and linkage studies.

# 2 Vaccination coverage

*E.A. van Lier*

Just as in previous years, at national level the average participation for all vaccinations included in the NIP was considerably above the lower limit of 90% for 2010. For the MMR vaccination, the lower limit used by the WHO is with 95% somewhat higher, to be able to eliminate measles worldwide. This lower limit was reached for the first MMR vaccination (babies) but not for the second MMR vaccination (9-year olds). Therefore, an outbreak of measles in the Netherlands is not impossible (see chapter 3.7).

The above results are stated in a report by the RIVM on vaccination coverage in the Netherlands in 2010. Included in the report are data on babies born in 2007, young children born in 2004 and schoolchildren born in 1999 (Table 4).[11]

For babies, participation in the MMR, Hib and meningococcal C vaccinations was 96%, for the DTaP-IPV vaccination 95% and for the pneumococcal vaccination 94%. Participation for hepatitis B vaccination among children of whom one or both parents was born in a country where hepatitis B occurs frequently, has increased further. The hepatitis B vaccination for children of mothers who are carrier of hepatitis B still requires some attention, since children who are infected with this virus at a young age have a higher risk of becoming a carrier of this virus and of contracting liver disorders in the long term.

Voluntary vaccination in the Netherlands results in a high vaccination coverage. High levels of immunisation are not only necessary in order to protect as many people individually as possible, but also to protect the population as a whole (herd immunity) against outbreaks of infectious diseases. Due to geographical and social clustering, herd immunity in the Dutch Bible belt region is insufficient and epidemics of NIP target diseases occur. Continuous efforts need to be made by all parties involved in the NIP to ensure that children in the Netherlands are vaccinated on time and in full.

**Table 4 Vaccination coverage per vaccine for age cohorts of newborns, toddlers, and schoolchildren in 2006-2010**

| | **Newborns*** | | | | **Toddlers*** | | | | **Schoolchildren*** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Report Year** | **cohort** | **DTaP -IPV** | **Hib** | **Pneu **** | **MenC** | **MMR** | **cohort** | **DTaP -IPV** | **cohort** | **DT -IPV** | **MMR ***** |
| 2006 | 2003 | 94.3 | 95.4 | - | 94.8 | 95.4 | 2000 | 92.5 | 1995 | 93.0 | 92.9 |
| 2007 | 2004 | 94.0 | 95.0 | - | 95.6 | 95.9 | 2001 | 92.1 | 1996 | 92.5 | 92.5 |
| 2008 | 2005 | 94.5 | 95.1 | - | 95.9 | 96.0 | 2002 | 91.5 | 1997 | 92.6 | 92.5 |
| 2009 | 2006 | 95.2 | 95.9 | 94.4 | 96.0 | 96.2 | 2003 | 91.9 | 1998 | 93.5 | 93.0 |
| 2010 | 2007 | 95.0 | 95.6 | 94.4 | 96.1 | 96.2 | 2004 | 91.7 | 1999 | 93.4 | 93.1 |

| | Newborns* | | |
|---|---|---|---|
| **Report Year** | **cohort** | **HBVa** | **HBVb** |
| 2006 | 2003 | 86.7 | 90.3 |
| 2007 | 2004 | 88.7 | 92.3 |
| 2008 | 2005 | 90.7 | 97.4 |
| 2009 | 2006 | 92.9 | 95.6 |
| 2010 | 2007 | 94.2 | 97.2 |

* Vaccination coverage is assessed at ages of 2 years (newborns), 5 years (toddlers), and 10 years (schoolchildren)

** Only for newborns born on or after 1 April 2006

*** Two MMR vaccinations (in the past 'at least one MMR vaccination' was reported)

[a] Children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic

[b] Children of whom the mother tested positive for HBsAg

# 3 Current National Immunisation Programme

## 3.1 Diphtheria

*F. Reubsaet, G. Berbers, F.R. Mooi, N.A.T. van der Maas*

### *3.1.1 Key points*

- In 2008-2009, no cases of diphtheria were reported in the Netherlands.

### *3.1.2 Changes in vaccine 2009-2010-2011*

In 2010 the following diphtheria containing vaccines were used for the NIP: infants received Pediacel (SPMSD), except those at risk of Hepatitis B, who received Infanrix Hexa (GSK). At the age of 4, Infanrix-IPV (GSK) was used as a pre-school booster. Nine-year-old children received dT-IPV (NVI).

### *3.1.3 Epidemiology*

In the period from 2009 week 32 until 2010 week 40, no cases of diphtheria have been notified.[12]

### *3.1.4 Pathogen*

In July 2010, a strain isolated from the skin of 20-year-old woman, suspected to have skin diphtheria was send to the RIVM; the strain was identified as *Corynebacterium diphtheriae* Gravis. The TOBI test gave 0.52 IU/ml. In September, from a nose isolate of a patient, female 51 years old, with chronic sinusitis, *C. diphtheriae* Belphanti was cultured and toxin tests were sent to the RIVM. Both strains were negative in the toxin PCR and ELEK test. Travelling history was not reported.

**Table 5 Diphtheria strains reported in the Netherlands**

| Year | Age (Yrs) | Sex | Source | Diagnosis | Tox-PCR | Elek-test |
|---|---|---|---|---|---|---|
| 2000 | 68 | f | nose | *Corynebacterium diphtheriae* Belfanti | neg | neg |
| 2001 | 49 | m | nose | *Corynebacterium diphtheriae* Belfanti | neg | neg |
| 2001 | 58 | m | throat | *Corynebacterium ulcerans* | pos | pos |
| 2002 | 78 | m | bronchial wash | *Corynebacterium diphtheriae* | neg | neg |
| 2003 | 69 | m | throat | *Corynebacterium diphtheriae* | neg | neg |
| 2004 | - | f | rhesus monkey | *Corynebacterium ulcerans* | pos | pos |
| 2005 | 53 | f | sputum | *Corynebacterium diphtheriae* Belfanti | neg | neg |
| 2007 | 26 | f | lymfangitis digit | *Corynebacterium ulcerans* | pos | pos |
| 2008 | 13 | m | nose | *Corynebacterium diphtheriae* Belfanti | neg | neg |
| 2008 | 67 | f | erysipelas | *Corynebacterium diphtheriae* Mitis/Intermedius | neg | neg |
| 2010 | 20 | F | Skin | *Corynebacterium diphtheriae* Gravis | neg | neg |
| 2010 | 51 | F | Nose | *Corynebacterium diphtheriae* Belphanti | neg | neg |

### *3.1.5 Adverse events*

For national data, see section 2.2.5.

Jackson et al. performed a vaccine safety data linkage study and found an increased risk of local reactions within one week following immunisation in persons who received a tetanus and diphtheria toxoid containing vaccine in the five years before the booster, compared with people who did not receive such a vaccine. However, the overall estimated risk was low, amounting 3.6 events per 10,000 Td vaccinations.[13]

### *3.1.6 Current/ongoing research*

No specific diphtheria-related research is ongoing. Routine surveillance is in place for signal detection.

## 3.2 Pertussis

*F.R. Mooi, S.C. de Greeff, G.A.M. Berbers, G.P.J.M. van den Dobbelsteen, N.A.T. van der Maas.*

### *3.2.1 Key points*

- The emergence of more virulent strains and escape variants which do not produce two important components of pertussis vaccines, pertussis toxin and pertactin, are worrying developments that underline the importance of surveillance in general and strain surveillance in particular, and the need to improve pertussis vaccines. Strains which do not produce pertactin, a component of most pertussis vaccines, have now been isolated in both France and Japan. Furthermore, in France, B. parapertussis strains

devoid of pertactin have also been isolated. As yet, strains devoid of proteins used in pertussis vaccines have not been found in the Netherlands.

- The circulation of pertussis among adolescents and adults more than doubled in the past decade. However, the highest morbidity and mortality due to pertussis is found in 0-6 months old infants who are too young to be fully vaccinated. A study on the direct costs of pertussis carried out by the RIVM suggests that cocooning vaccination will be more attractive than vaccination.
- A higher frequency of (severe) local reactions after the booster vaccination with a combined diphtheria, tetanus and acellular pertussis vaccine (dTaP) at 4 years of age was observed for those cohorts that received acellular pertussis vaccine in the primary series.
- The spacing between the primary series (2, 3, 4, and 11 months) and the booster at 3-4 years was based on whole cell pertussis vaccination. With the introduction of a more effective acellular pertussis vaccine, the booster could possibly be delayed until a slightly older age. This will possibly increase the duration of protection and might also reduce side effects.

### *3.2.2 Changes in vaccine 2009-2010-2011*

In 2010 the following pertussis containing vaccines were used for the NIP: infants received Pediacel (SPMSD) except those at risk for Hepatitis B, who received Infanrix Hexa (GSK). At the age of 4, Infanrix-IPV (GSK) was used as a pre-school booster.

### *3.2.3 Epidemiology*

Since the sudden upsurge in 1996-1997, the incidence of reported and hospitalised pertussis cases has remained high. Peaks in reported cases were observed every 2-3 years (i.e., in 1999, 2001, 2004 and 2008) (Figure 1). The largest increase in pertussis was observed in adolescents and adults. Based on notifications until June, the extrapolated incidence in 2010 is lower than in 2008 and 2009. Since the sudden upsurge in 1996-1997, the incidence of reported and hospitalised pertussis cases has remained high. However, hospitalisations show a decreasing trend since the introduction of the preschool booster. Interpretation of this trend is hampered by changes in coverage of the hospital admission database (see methods) and the introduction of a case-mix system, known as the DBC system, whereby DBC stands for Diagnose (Diagnosis), Behandel (Treatment) Combinatie (Combination). Peaks in reported cases were observed every 2-3 years (i.e., in 1999, 2001, 2004 and 2008) (Figure 1). The largest increase in pertussis was observed in adolescents and adults. Based on notifications until June, the extrapolated incidence in 2010 is lower than in 2008 and 2009.

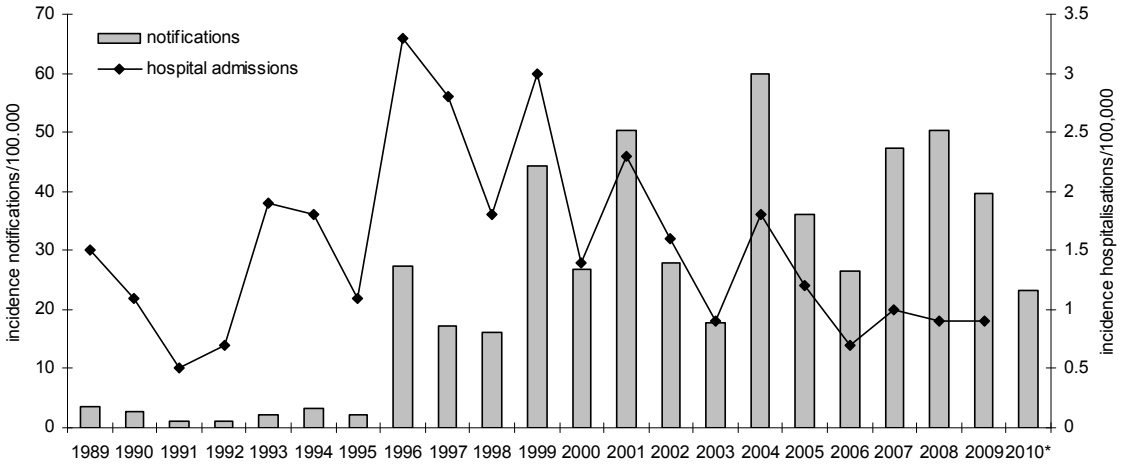
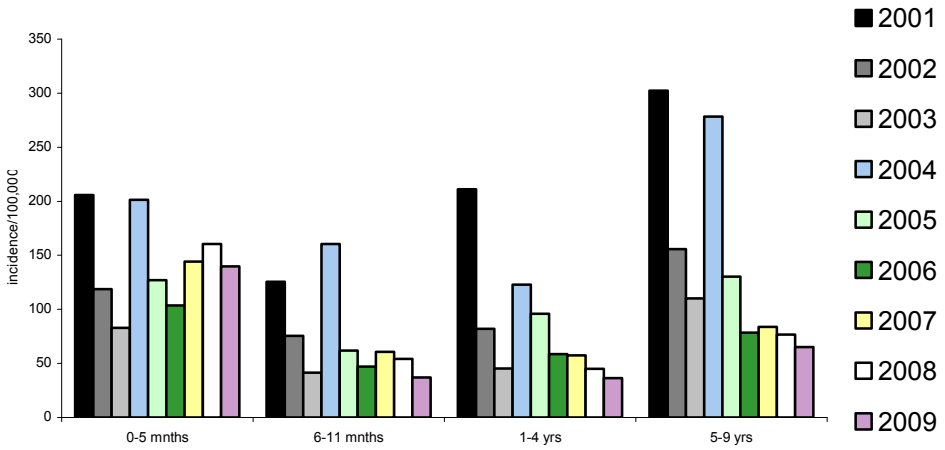



**Figure 1 Incidence of pertussis notifications (grey bars) and hospitalisations (line) by year in 1989-July 2010. * Notifications in 2010 were extrapolated for a whole year. Data for hospitalisations are not yet available for 2010**

The introduction of the preschool booster vaccination for 4-year-olds with an acellular vaccine in the autumn of 2001 caused a significant decrease in the incidence of pertussis among the targeted population (Figure 2A).

Since the replacement of the whole cell vaccine by an acellular vaccine in 2005, the average annual incidence in recently vaccinated children aged 6 mths-4 years (not yet eligible for the preschool booster) has decreased, suggesting an increase in vaccine efficacy. In the same period, the incidence of notifications for pertussis among adolescents and adults increased, most notably in the age category 10-19 years (Figure 2B).



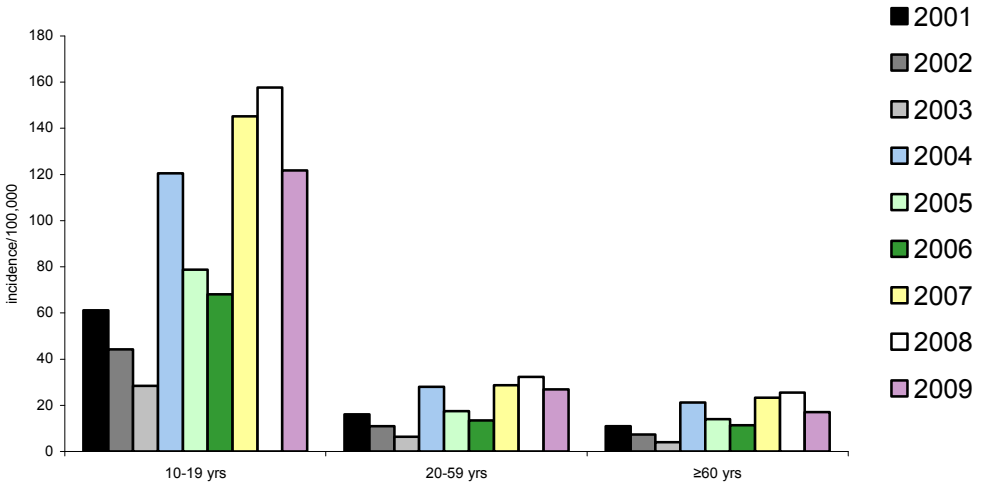



**Figure 2 Average annual incidence of notifications for pertussis among children <10 years of age (Figure 2A) and adolescents and adults (Figure 2B), in 2001-2009**

3.2.3.1 Sero-epidemiology

Trends in epidemiology are confirmed by trends in sero-epidemiology. In a cross-sectional population-based sero-surveillance study conducted in 2006-07 (PIENTER, N=8000), it was estimated that 9.3% (95%CI 8.5-10.1) of the population above 9 years of age had an IgG-Ptx concentration above 62.5 EU/ml, which is suggestive of pertussis infection in the past year. This percentage more than doubled compared to 1995-96 (4.0%; 95%CI 3.3-4.7). In both periods, about a quarter of the individuals with a presumptive pertussis infection reported that they had experienced a period of at least 2 weeks of coughing in the preceding year.

3.2.3.2 Burden of disease

Since 1996, ten children have died from pertussis: two in 1996, two in 1997, one in 1998, three in 1999, one in 2004 and one in 2006. In 2008, one elderly woman (aged 75-80) died. All deceased children were less than 3 months of age, except for a girl in 2006 who was 11 years old. The girl was asthmatic and both mentally and physically handicapped. These conditions may have contributed to the severity of pertussis and her death.

Since 1999-2001 the number of infants <6 months hospitalised for pertussis shows a decreasing trend (Figure 3). Presumably, transmission from siblings to susceptible infants has been reduced as a result of the preschool booster administered since 2001. Since the replacement of the whole cell vaccine by the acellular vaccine in 2005, the incidence of hospitalisation for children aged 6-11 months and 1-3 years has reduced by almost 60%. For infants less than 6 months of age, a less sharp reduction (20%) was observed (Figure 3). Since most hospitalisations concern young children, the impact of these changes in vaccination strategies also seems to have resulted in a slightly decreasing trend in hospitalisations in recent years.

Interestingly, a follow-up of infants in the Binki study who were hospitalised for pertussis in infancy showed that these children are at higher risk of respiratory morbidity at toddler age compared to a control-group.[14] The higher risk of respiratory illness in childhood may be a precursor for asthma in adulthood. The mechanisms that underlie this association require further investigation.

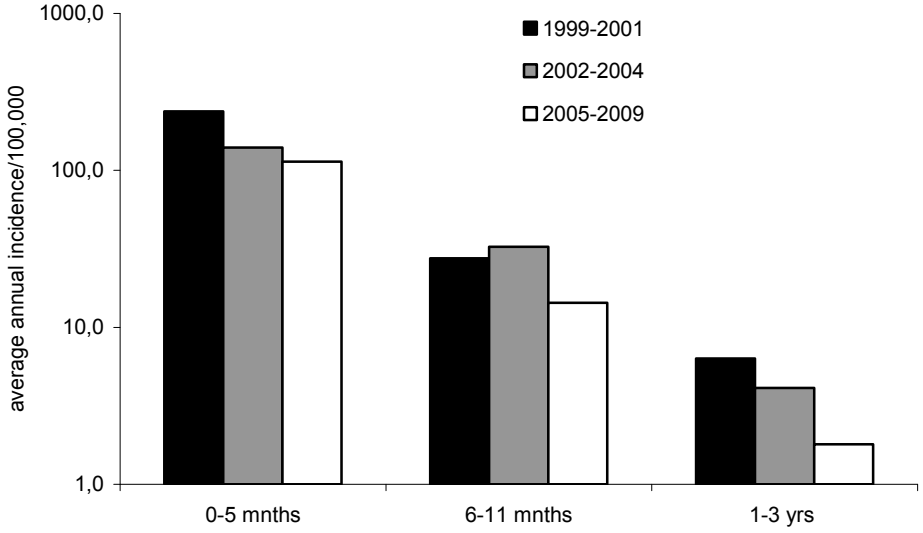



**Figure 3 Average annual incidence (log-scale) of children hospitalised for pertussis by age group and per period 1999-2001 (no preschool booster), 2002-2004 (preschool booster given to 4-year olds) and 2005-2009 (acellular vaccine in use)**

### 3.2.3.3 Vaccine effectiveness

In Table 6 the vaccine effectiveness estimated with the 'screening method' is shown. The vaccine efficacy (VE) was estimated according to Equation 1:

VE (%) = 1 - [PCV / (1 - PCV) * (1 - PPV) / PPV]

**Equation 1: PCV = proportion of cases vaccinated, PPV = proportion of population vaccinated, and VE = vaccine efficacy**

For some age groups, the proportion of vaccinated individuals exceeded the estimated vaccine coverage of the population (96%). Therefore, VE could not be estimated (indicated by '–').
We would like to emphasise that the presented VE should not be interpreted as 'true' absolute efficacies. They are used to study trends in VE estimations. In the years before 1996 vaccine effectiveness was higher than after the epidemic of 1996. In recent years, the VE is increasing again. The higher VE since 2006-2007 for 1-3-year-olds, possibly points at better protection of this group by the acellular vaccine.

**Table 6 Estimation of vaccine effectiveness (%) by the 'screening method' for 1-3-year-olds per year**

| Age | '93 | '94 | '95 | '96 | '97 | '98 | '99 | '00 | '01 | '02 | '03 | '04 | '05 | '06 | '07 | '08 | '09 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 Yr | 94 | 77 | 91 | 31 | 29 | 38 | 63 | 78 | 73 | 63 | 29 | 54 | 72 | 87 | 92 | 90 | 90 |
| 2 Yrs | 92 | 58 | 42 | 63 | - | 32 | 22 | 52 | 46 | 41 | - | - | 67 | 58 | 92 | 91 | 89 |
| 3 Yrs | 85 | 79 | 60 | 38 | - | 10 | - | - | - | 54 | 10 | 37 | 59 | 43 | 84 | 82 | 83 |

We also estimated the vaccine effectiveness of the preschool booster vaccination with the 'screening method' (Table 7), assuming a vaccination coverage of 92%.[11] The decreasing vaccine effectiveness for the oldest birth cohort suggests immunity wanes within 5-7 years.

**Table 7 Vaccine effectiveness (%) of the preschool booster by birth cohort**

| Year of birth | VE |
|---|---|
| 1998 | 0 |
| 1999 | 0 |
| 2000 | 36 |
| 2001 | 47 |
| 2002 | 51 |
| 2003 | 61 |
| 2004 | 84 |
| 2005 | 90 |

### *3.2.4 Pathogen*

As observed in previous years, P3 *Bordetella pertussis* strains predominated in 2010. These strains were found at a frequency of 90% (range 72% to 100%) from January 2004-October 2010. P3 strains produce more pertussis toxin than P1 strains, which predominated in the 1990s, and there is evidence that this has increased the virulence of the P3 strains.[15] Like the P1 strains, P3 strains show (small) differences in antigenic make-up in pertussis toxin and pertactin compared to pertussis vaccines.[16] A notable trend observed in the last two years is the replacement of serotype 3 fimbriae strains by serotype 2 fimbriae strains. Serotype 2 fimbriae strains increased in frequency from 4% in 2007 to 100% in 2010. The relevance of this shift in serotype is not clear, especially as the current pertussis vaccine does not contain fimbriae. Strains which do not produce one or more vaccine components have been identified in France, Japan and Sweden.[17-20] As yet, such strains have not been found in the Netherlands.[19]

### *3.2.5 Adverse events*

The enhanced spontaneous reporting system, in place at Cib, receives AEFI for all vaccines covered by the NIP. The number of reports following DTaP-IPV-Hib, combined with an HBV component for certain risk groups, was 757. Range for 2005-2008 was 593-736. The reporting rate for infant vaccinations at 2, 3, 4 and 11 months was stable for 2005-2009. For the second consecutive year, both the absolute number and the reporting rate of AEFI following dTaP-IPV booster vaccination at 4 years of age has increased, due to more reports of local reactions and/or fever (Figure 4).[21]

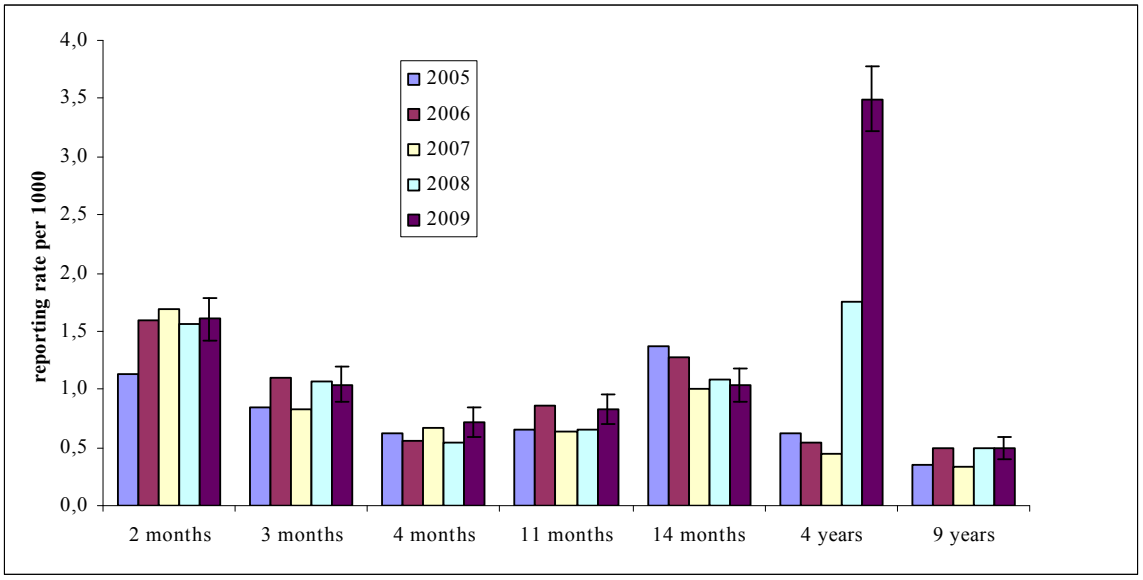



**Figure 4 Reporting rate per 1,000 vaccinated children per dose**

All children eligible for DTaP-IPV vaccination at 4 years of age in 2009 had primary series with acellular DTP-IPV-Hib vaccine. In 2008 this was only the case for a small part of the cohort. This higher risk on local reactions and fever after booster doses of DTP-IPV is described in the literature.[22-24] Two questionnaire studies on reactogenicity of this booster DTaP-IPV were performed in the Netherlands in 2008 and 2009. The results will be published in 2011 and they reveal accurate incidence rates of local reactions and fever and address the influence of preceding vaccinations with or without acellular pertussis. With the introduction of a more effective ACV, the booster could possibly be delayed until a slightly older age. This will possibly increase the duration of protection and might also reduce side effects. Furthermore, vaccines with reduced antigen content may decrease the reactogenicity of booster vaccinations. A review of the Cochrane Collaboration, published in 2010, found that minor adverse events were more common in children administered with a combined DTaP-Hib-HepB vaccine compared with separate administration of Hib and HepB. Serious adverse events were comparable between the groups.[25]

Huang et al. found no association between acellular pertussis vaccine and seizures in early childhood, using risk-interval cohort and self-controlled case series (SCCS) analysis. The adjusted incidence rate ratio was 0.87 (95%CI 0.72-1.05) and 0.91 (95%CI 0.75-1.10) in the cohort and SCCS analysis, respectively.[26]

For adolescents receiving dTaP vaccines, a study of Klein et al. found no increased risk for neurologic, hematologic or allergic events, nor for the new onset of chronic illnesses.[27]

### *3.2.6 Current/ongoing research*

The emergence of escape mutants in the Netherlands which do not produce pertactin or other vaccine components will be closely monitored.The spread and prevalence of these strains in Europe will be determined in collaboration with EU partners. By comparing vaccination programmes with surveillance data between European countries, optimal vaccination strategies will be identified to decrease the circulation of *B. pertussis* and limit the emergence of escape mutants. For example, we will investigate whether there is a relationship between the number of components in acellular vaccines and the prevalence of escape mutants.

The efficacy of the current vaccination programme and the effect of recent changes in vaccines will be monitored based on hospitalisations and notifications. Furthermore, we will assess the duration of immunity conferred by the booster given to 4-year-old children.

A study on the direct costs of pertussis carried out by the RIVM[28] suggests that cocooning vaccination will be more attractive from an economical point of view than repetitive adolescent and adult vaccination. To facilitate the decision-making regarding the introduction of cocooning a cost-effectiveness evaluation of this strategy will be conducted.

To evaluate the potential impact of adolescent or adult booster vaccination strategies, more insight into the disease burden and severity of pertussis in adults would be valuable. Furthermore, our finding that infants in the Binki study who were hospitalised for pertussis in infancy are at higher risk for respiratory morbidity at toddler age compared to a control group requires further investigation.

## 3.3 Tetanus

*S.J.M. Hahné, H.E. de Melker, D. Notermans*

### *3.3.1 Key points*

- Tetanus is again notifiable since December 2008.
- In 2009, one case of tetanus was notified, in an incompletely vaccinated man.
- Immunity in the Dutch population against tetanus is adequate. However, a recent sero-epidemiological study identified some risk groups.

### *3.3.2 Changes in vaccine 2009-2010-2011*

The most recent change in the NIP that affected tetanus vaccination was the introduction of the MenC vaccination, with tetanus-toxoid as a carrier protein, in 2002 for all children at 14 months of age and all individuals aged 1-18 years. The effects of this were observed in immunosurveillance (see below).

### *3.3.3 Epidemiology*

In 2009 one case of tetanus was notified. This concerned a 60-year-old man, who was incompletely vaccinated. He had received two DTP vaccinations in the past, the last one in 2001. He was most likely infected during his occupation, as a flower-bulb farmer. The patient survived. In 2010, up to week 44, 2 cases of tetanus were notified: A 77-year-old woman and a 71-year-old man. Both were unvaccinated and both survived after hospitalisation.

*Immunosurveillance*

Results of the national seroprevalence study Pienter II (2006/2007) suggest that immunity in the general Dutch population is adequate. Lower seroprevalences were, however, found in individuals born before the introduction of routine vaccination, first-generation migrants from non-Western countries born before 1984 and conservative Protestants living in the Dutch 'Bible belt'.

Only 10% of those eligible for post-exposure prophylaxis were not sufficiently protected against tetanus.

The tetanus-toxoid antibody concentration was increased with age in the age-cohorts of 13–23 years, which coincides with the meningococcal conjugate mass-vaccination in 2002.[29]

### *3.3.4 Pathogen*

No relevant information to be reported.

### *3.3.5 Adverse events*

See paragraph 2.2.5.

### *3.3.6 Current/ongoing research*

The NVI is carrying out research regarding the development of analytical test systems for tetanus vaccine, which could be an alternative for animal testing.

Given the very high level of protection against tetanus in the Dutch population, the effectiveness and safety of offering post-exposure vaccination only to specific groups could be explored in a study in which, for all persons who visit clinics because of an injury, the TT-antibody concentration is first determined using a rapid immunochromatographic test before offering vaccination. If effective and safe, such an alternative strategy would enable a reduction of booster vaccinations. Furthermore, the feasibility and cost-effectiveness of offering vaccination to individuals who were not eligible for routine vaccination in the past due to their advanced age and for first-generation migrants from non-Western countries who are born before 1983, should be explored.[29]

## 3.4 Poliomyelitis

*H.G.A.M. van der Avoort, W. Bakker, N.A.T. van der Maas*

### *3.4.1 Key points*

- In 2008-2009, no cases of polio were reported in the Netherlands.
- The total number of cases in the four traditional endemic countries (Nigeria, Northern India, Afghanistan and Pakistan) has fallen dramatically in the last two years, and is much lower than the number of cases due to importations from these countries.
- The polio-free status of the European Region of the WHO (declared on June 21st, 2002) is at stake, due to an epidemic originated in Tajikistan and spread to Kazakhstan, Turkmenistan, the Russian Federation and most likely also to Uzbekistan.
- The notification of cases in the Caucasus region of the Russian Federation is of importance for the Netherlands, as this region neighbours Turkey, the origin of the viruses that caused the last two poliomyelitis outbreaks in the Netherlands (1978 and 1992/3).
- The definition of vaccine derived polioviruses (VDPVs) has been adapted. Any type 2 poliovirus with 6 or more changes from Sabin 2 will be considered a "vaccine-derived poliovirus" of programmatic importance, regardless of its source; the definition of type 1 and type 3 VDPVs remains unchanged (≥ 10 changes in VP1)

### *3.4.2 Changes in vaccine 2009-2010-2011*

In 2010 the following inactivated polio viruses containing vaccines were used for the NIP: infants received Pediacel (SPMSD) except those at risk for Hepatitis B, who were administered with Infanrix Hexa (GSK). At the age of 4, Infanrix-IPV (GSK) was used as a pre-school booster. 9-year-old children received dT-IPV (NVI).

#### 3.4.2.1 Intradermal administration of IPV.

Given the increasing amount of evidence that use of OPV under particular circumstances, i.e., low OPV coverage in countries where at least one of the three serotypes has been eradicated or when administrated to an immuno-compromised person, might give rise to virus circulation and epidemics of poliomyelitis, new ways for cheaper but safe, administration of IPV in developing countries are being evaluated at the moment.

A multicenter clinical trial of fractional doses of IPV was conducted in Oman.[30] The immunogenicity and reactogenicity of a fractional dose IPV (0.1 ml or 1/5 of a full dose) given intradermally by a needle-free jet injector device was compared to that with full doses given intramuscularly. Fractional doses of IPV given intradermally by needle-free device at two, four, and six months induced similar levels of seroconversion as full doses of IPV given intramuscularly. The median titres were significantly lower but still sufficient for full protection in the intradermal arm, as was resistance to poliovirus excretion following a challenge dose

given at seven months. Trials like the Oman study indicate that IPV under the circumstances described can be a good candidate for safe mass vaccination in developing countries.

### *3.4.3 Epidemiology*

3.4.3.1 Polio eradication initiative: global situation in 2010.

The global status of polio eradication has changed dramatically in 2009 and 2010. A more than 50-fold drop in poliomyelitis incidence in Nigeria, due to the successful implementation of national and sub-national immunisation campaigns with bivalent (type 1 +3) OPV next to the usual trivalent OPV, have also lowered the risks for importation to neighbouring countries. Most of these countries are polio-free again, after stopping poliovirus circulation after import from the Nigerian reservoir before 2010.

Similar success is seen in northern India: a more than tenfold reduction in number of cases in 2010 compared to the same period in 2009 (including the traditional high incidence rainy season) with only localised circulation in some parts of northern India.

On the negative side, transmission in Afghanistan and Pakistan continues at higher levels, due to the large floods and the increase in political unrest. Nevertheless, the total number of cases in the four traditional endemic countries has fallen dramatically, and is much lower than the number of cases due to importations from these countries.

Circulation of polio type 1 virus in Central Africa after import from India is still ongoing. The biggest outbreak of poliomyelitis, also after import from polio type 1 virus from India, has been observed in Tajikistan with 458 cases and has spread to Kazakhstan, Turkmenistan, the Russian Federation, and most likely also to Uzbekistan (Figure 5). The polio-free status of the European Region of the WHO (declared on June 21$^{st}$, 2002) is at stake, unless countries can stop circulation within six months after the first detected case. In all countries (and in neighbouring countries with vaccination coverage too low to stop circulation), additional vaccination campaigns are organised to stop or prevent the circulation of poliovirus. The notification of cases in the Caucasus region of the Russian Federation is also of importance for the Netherlands, as this region neighbours Turkey, the origin of the viruses that caused the last two poliomyelitis outbreaks in the Netherlands (1978 and 1992/3).

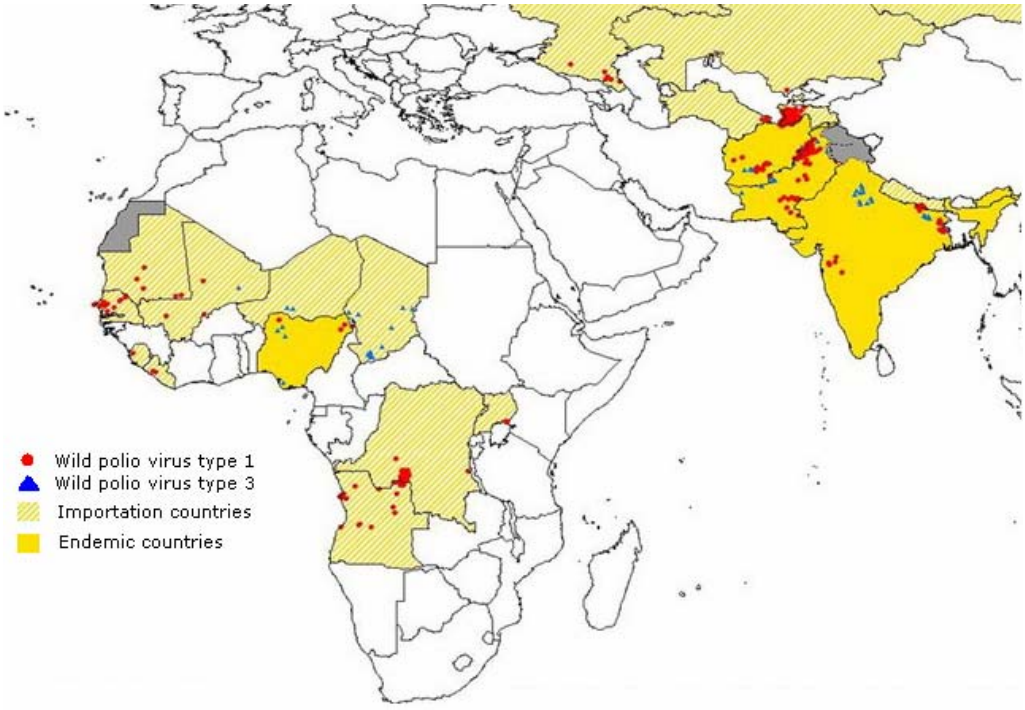



**Figure 5 Poliomyelitis incidence (WHO; Data at HQ as of 26 October 2010)**

The world-wide poliovirus eradication campaign requires that in the final stages of eradication a switch is made from live oral polio vaccine to inactivated polio vaccine because of the risk of emerging VDPVs. At the request of WHO, NVI is currently setting up a process to use the strains used for the production of oral live polio vaccine (OPV) for the production of inactivated polio vaccine (Sabin-IPV), based on the current NVI Salk-IPV production technology. The aim is to produce clinical trial materials, scale-up and technology transfer to vaccine manufacturers meeting WHO defined criteria in low and middle–income countries. The overall goal is to aid in the eradication of poliovirus.

### *3.4.4 Pathogen*

Since the first description of circulating vaccine derived polioviruses (cVDPVs), causing outbreaks of poliomyelitis indistinguishable from wild-type epidemics (Hispagniola 2002), these viruses have been characterised in 12 more instances (Table 8). A common feature in all these cVDPVs was at least 10 nucleotides difference in the VP1 gene compared to the OPV seed strain. However, there is compelling, new evidence for the circulation of type 2 Sabin-derived polioviruses with fewer than 10 changes in VP1, suggesting that viruses with fewer changes may be relevant to polio surveillance and eradication. Therefore, any type 2 poliovirus with six or more changes from Sabin 2 will be considered a "vaccine-derived poliovirus" of programmatic importance, regardless of its source; the definition of type 1 and type 3 VDPVs remains unchanged (≥ 10 changes in VP1).

**Table 8 Circulating vaccine-derived Poliovirus, 2000-2010 (WHO, data in WHO/HQ as of 12 Oct 2010)**

| Country | Type | cVDPV | | | | | | | | | | | First case | Last case |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | | |
| Nigeria | VDPV 2 | - | - | - | - | - | 1 | 21 | 68 | 63 | 153 | 16 | 02-Jul-05 | 26-Aug-10 |
| D R Congo | VDPV 2 | - | - | - | - | - | - | - | - | 14 | 4 | 8 | 22-Mar-08 | 13-Aug-10 |
| Afghanistan | VDPV 2 | - | - | - | - | - | - | - | - | - | - | 3 | 10-Jun-10 | 02-Jul-10 |
| Niger | VDPV 2 | - | - | - | - | - | - | 2 | - | - | - | 1 | 28-May-06 | 01-Jun-10 |
| Ethiopia | VDPV 3 | - | - | - | - | - | - | - | - | - | 1 | 5 | 27-Apr-09 | 17-May-10 |
| India | VDPV 2 | - | - | - | - | - | - | - | - | - | 15 | 1 | 14-Jun-09 | 18-jan-10 |
| Somalia | VDPV 2 | - | - | - | - | - | - | - | - | 1 | 4 | - | 29-Jun-08 | 24-Dec-09 |
| Guinea | VDPV 2 | - | - | - | - | - | - | - | - | - | 1 | - | | 06-May-09 |
| Ethiopia | VDPV 2 | - | - | - | - | - | - | - | - | 3 | 1 | - | 04-Oct-08 | 16-Feb-09 |
| Myanmar | VDPV 1 | - | - | - | - | - | - | 1 | 4 | - | - | - | 09-Apr-06 | 06-Dec-07 |
| Cambodia | VDPV 3 | - | - | - | - | - | 1 | 1 | - | - | - | - | 26-Nov-05 | 15-Jan-06 |
| Indonesia | VDPV 1 | - | - | - | - | - | 46 | - | - | - | - | - | 09-Jun-05 | 26-Oct-05 |
| Madagascar | VDPV 2 | - | 1 | 4 | - | - | 3 | - | - | - | - | - | | 13-Jul-05 |
| China | VDPV 1 | - | - | - | - | 2 | - | - | - | - | - | - | 13-Jun-04 | 11-Nov-04 |
| Philippines | VDPV 1 | - | 3 | - | - | - | - | - | - | - | - | - | 15-Mar-01 | 26-Jul-01 |
| D OR/Haiti | VDPV 1 | 12 | 9 | - | - | - | - | - | - | - | - | - | 12-Jul-00 | 12-Jul-01 |

### *3.4.5 Adverse events*

For national data, see section 2.2.5.

A retrospective cohort study on paralytic syndromes in children, carried out in the United States, revealed an incidence of 1.4 / 100,000 children*year (95% CI 1.2-1.6). No cases of vaccine-associated acute flaccid paralysis were identified. Therefore, it is difficult to use flaccid paralysis surveillance in non-endemic countries to identify the risk of poliovirus importation.[31]

### *3.4.6 Current/ongoing research*

No specific poliomyelitis-related research is ongoing at RIVM, routine surveillance is in place for signal detection.

## 3.5 *Haemophilus* influenzae serotype b (Hib) disease

*S.C. de Greeff, L.M. Schouls*

### *3.5.1 Key points*

- There have been no significant changes in the number or nature of invasive disease cases caused by *Haemophilus influenzae* serotype b in 2009 in the Netherlands.
- No changes in composition and characteristics of the Hib strains causing invasive disease have been observed.

### *3.5.2 Changes in vaccine 2009-2010-2011*

There have been no changes in the composition or vaccination schedule for Hib and no changes are anticipated in the near future.

### 3.5.3 *Epidemiology*

*Disease*

Since the introduction of vaccination in 1993, the number of patients with Hib disease has decreased from 250 cases in 1993 to 12 cases in 1999 (Figure 6, Figure 7). However, in 2002-2005 the number of patients with Hib disease increased significantly, with a peak of 48 cases in 2004. Since then, the annual number of cases has decreased again to approximately 25 cases annually (Figure 6). In 2009 the number of cases amounted to 32. The reason for the upsurge in cases of invasive Hib disease in 2002-2005 has remained enigmatic.

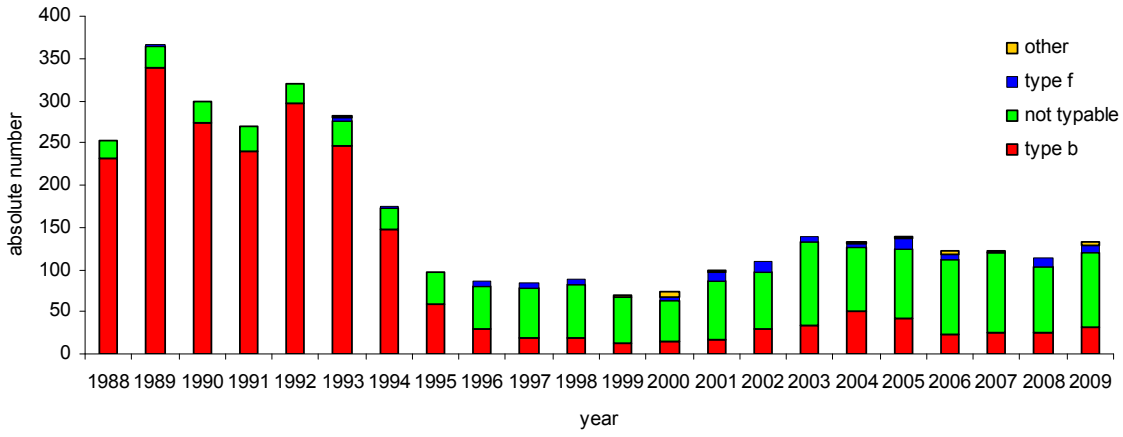



**Figure 6 The absolute number of *H. influenzae* isolates by serotype, 1988-2009**

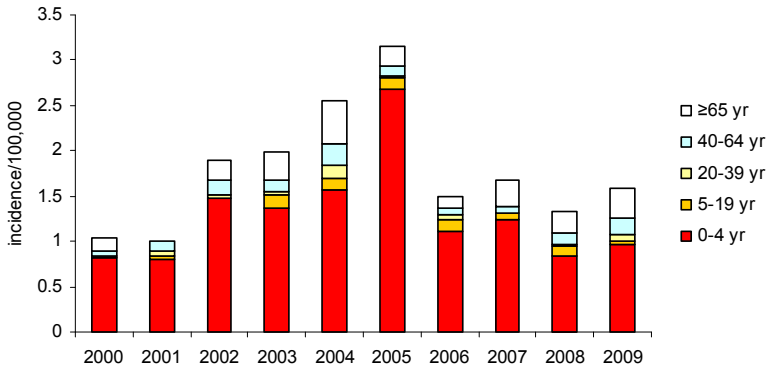



**Figure 7 The age-specific incidence of patients with invasive Hib disease by year**

*Vaccine effectiveness*

In the vaccinated cohorts, the number of infections due to Hib and the number of vaccine failures showed a peak in 2005 but the number decreased again in the following years (Figure 8; the annual incidence per 100,000 is shown in Figure 7).

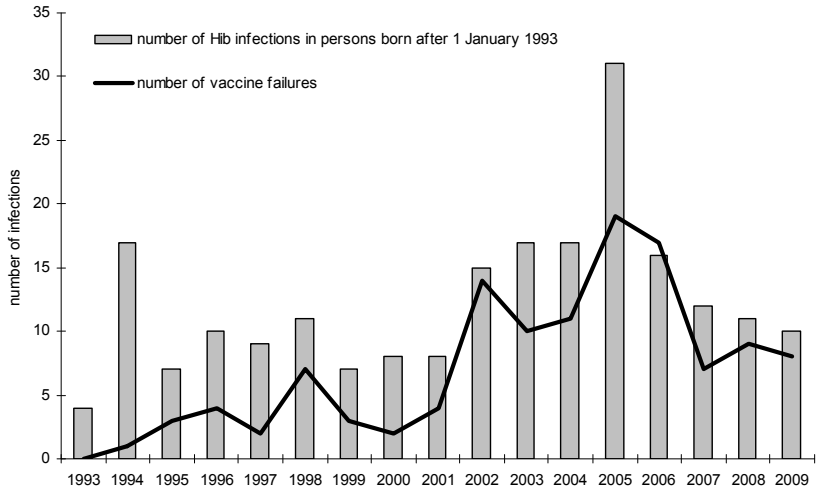



**Figure 8 The annual number of Hib infections in persons eligible for vaccination (i.e., born after 1 January 1993) and the number of vaccine failures**

*Immune surveillance*

Currently immune surveillance data on the prevalence of antibodies directed against Hib are being analysed. In this analysis, data from the Pienter I collection are compared to those obtained from the Pienter II collection.

### *3.5.4 Pathogen*

No change in the composition of the *H. influenzae* population circulating in the Netherlands has been observed.

### *3.5.5 Adverse events*

See section 2.2.5

### *3.5.6 Current/ongoing research*

Surveillance of invasive *H. influence* infections and typing of the *H. influence* strains is ongoing.

## 3.6 Mumps

*S.J.M. Hahné, R.S. van Binnendijk, N.A.T. van der Maas*

### *3.6.1 Key points*

- In early 2009 the genotype D mumps virus disappeared from the low vaccine areas, whilst new outbreaks of the genotype G virus occured in vaccinated students in 2010.
- Studies into vaccine effectiveness and reasons for vaccine failure have been initiated.

### *3.6.2 Changes in vaccine 2009-2010-2011*

No changes have occurred in the MMR vaccine used in the NIP during 2009 compared to 2008.

### *3.6.3 Epidemiology*

In 2009, 78 cases of mumps were notified. The age of cases ranged between 1 and 56 years, with a median of 19 years. 2009 was the first year mumps was notifiable again (after 1999), so recent reference data are not available. The mumps outbreak in the low vaccine coverage areas stopped in early 2009, with the last case caused by the outbreak strain (genotype D) identified in May 2009.[32]

For 73 of the 78 cases in 2009, information on their vaccination status was reported. Of these, 44% (32) were vaccinated. Of the 41 unvaccinated cases, 51% reported this was due to religious objections. For seven cases it was reported they were hospitalised.

In December 2009, the Municipal Health Service in South Holland West reported a cluster of mumps cases among students. This outbreak continued in 2010 and involved mainly students in several "university" cities.[33] In 2010 up to week 44, 391 mumps cases were reported, including seven hospitalisations. The majority of cases in this outbreak are fully (2x) vaccinated individuals, raising concerns about vaccine effectiveness and reasons for vaccine failure. Outbreaks in vaccinated adolescents have been reported from many countries. Explanations include low vaccine efficacy and waning of vaccine induced immunity.[34] Control of the outbreak involved offering MMR vaccine to unvaccinated or incompletely vaccinated students.

### *3.6.4 Pathogen*

The mumps strain circulating during the 2007-2009 outbreak among unvaccinated individuals in low vaccine coverage areas was genotype D. The strain involved in the student outbreak that started in the second half of 2009 was genotype G, which is the same genotype causing many of the mumps outbreaks in vaccinated communities abroad.

### *3.6.5 Adverse events*

In the Netherlands in 2009 the number of AEFI following Mumps Measles Rubella (MMR) vaccination was 280, compared with 233-315 for 2005-2008. Mostly MMR vaccination is simultaneously administered with either MenC vaccination at 14 months of age or dT-IPV booster at 9 years of age. The reporting rate for both vaccination moments has been rather stable for the last 5 years.[21] (Figure 4)

Sharma et al. conducted a prospective post-marketing safety study, using a MMR vaccine containing the Leningrad-Zagreb strain as mumps component. They found no association with aseptic meningitis after vaccination of more than 450,000 Egyptian children aged 16-24 months or 5-7 years.[35]

In early 2010, the Lancet retracted a paper they published in 1998 by Wakefield et al., in which a link was suggested between MMR vaccination and autism. The paper was shown to be incorrect.[36]

### *3.6.6 Current/ongoing research*

The 2007-2009 outbreak in low vaccine coverage areas allowed the assessment of VE. For this purpose, a cohort study in eight primary schools was carried out. Results are analysed by epidemiological methods and mathematical modelling (Snijders et al., van Boven et al., unpublished data). Preliminary results from the epidemiological analyses suggest the VE in the studied primary school population against the genotype D strain was adequate (VE one dose 92% [95% CI 83-96%], two doses 94% [87-97%]). Determination of mumps IgG in oral fluid samples was part of the retrospective epidemiological study in schools, to identify possible asymptomatic mumps infections in the vaccinated group. A different cut-off to identify recent infection was used for vaccinated and unvaccinated individuals. The study suggested that between 8 and 11% of MMR vaccinated children had an asymptomatic mumps virus infection (Dittrich et al. 2010, in press).

The ongoing outbreak among vaccinated students raised questions about risk factors for vaccine failure. Preliminary results suggest that large household size and attending a particular student party in Leiden in early 2010 were risk factors (Greenland, unpublished data).

During 2011, the results of the Pienter II project into the population immunity against mumps will become available.

## 3.7 Measles

*S.J.M. Hahné, R.S. van Binnendijk*

### *3.7.1 Key points*

- The incidence of measles in 2009 was 0.9 / 1,000,000 population, which is below the WHO elimination target (1 / 1,000,000).
- The largest cluster occurred among persons with a critical attitude towards vaccination, attending a Montessori school (n=5).
- In 2009, a fatal measles case was reported, in an unvaccinated Scottish person who temporarily lived in the Netherlands and most likely contracted measles abroad.

### *3.7.2 Changes in vaccine 2009-2010-2011*

No changes have occurred in the MMR vaccine used in the NIP during 2009 compared to 2008.

### *3.7.3 Epidemiology*

In 2009, fifteen measles cases were reported (0.9 / 1,000,000 population). Of the fifteen cases five were hospitalized, of whom one died. The age of cases ranged between 0 and 43 years. For thirteen cases the vaccination status was known. Of these, twelve were unvaccinated and one was vaccinated once. Of the nine unvaccinated cases born after 1974 (i.e., eligible for vaccination), six were unvaccinated based on a critical attitude towards vaccination. No cases were reported in unvaccinated persons based on religious beliefs. The fatal measles case

concerned a 38-year-old, previously healthy, Scottish man temporarily living in the Netherlands. He most likely acquired measles during his travels in Thailand and was reportedly unvaccinated.
The largest cluster among the 15 cases was of four cases in the GGD region IJsselland. One additional case related to this cluster occurred in 2010, making the total cluster size five. The first case in this cluster was a teacher of a 'Montessori' school. Subsequent cases were a colleague, one of her female pupils, her brother and an epidemiologically unrelated case. From the latter case, the same virus genotype (D4) was isolated, indistinguishable from the 'Montessori' cluster.
The second cluster concerned four cases in one family who were unvaccinated based on a critical attitude towards vaccination. The virus was most likely introduced from Italy. Genotyping could not be performed as disease notification was too late. The smallest cluster concerned two non-Dutch residents on a passenger ship.[37]
In 2010, up to week 44, 11 cases have been notified.

### *3.7.4 Pathogen*

The wild-type measles virus genotype signatures were determined for eight of the fifteen notified cases (1: D8, 4: D9, 3: D4). Vaccine-associated genotype A virus was detected in the oropharyngeal specimens from a child, which developed measles symptoms five days after primary MMR vaccination.

### *3.7.5 Adverse events*

See paragraph 2.6.5

### *3.7.6 Current/ongoing research*

A study is planned into correlates for protection during the anticipated outbreak of measles in the low vaccination coverage areas (ZonMW project). This study will adopt cellular immune assays which were developed and tested in healthy adult volunteers vaccinated against measles as part of a strategic research project (SOR), and for which data evaluation and presentation will be finished by the end of 2010.
Further ongoing research concerns the development of mathematical tools to maximise inferences that can be drawn from serological data on measles, mumps, rubella and varicella, combined with data on contact patterns. The aim of this research is to recommend an optimal MMR vaccination strategy.

During 2011, the results of the Pienter II project into the population immunity against measles will become available.

## 3.8 Rubella

*S.J.M. Hahné, R.M. van Binnendijk*

### *3.8.1 Key points*

- The incidence of rubella was very low in 2009 (0.05 / 100,000).
- The largest cluster (n=5) occurred among persons with a critical attitude towards vaccination, attending a Steiner ('vrije') school.
- For none of the reported cases could a genotype be determined.

### *3.8.2 Changes in vaccine 2009-2010-2011*

No changes have occurred in the MMR vaccine used in the NIP during 2009 compared to 2008.

### *3.8.3 Epidemiology*

In 2009, nine cases of rubella were notified (incidence 0.05 / 100,000). Of these, five were clustered in two families in South Limburg, with children attending the same anthroposophic secondary school (a 'vrije' school). None of the five cases were vaccinated, for three of them reportedly due to a critical attitude towards vaccination. There were no cases of rubella in pregnancy or CRS reported. The age of the nine cases ranged from 14 to 55 years. None was vaccinated. In 2010, up to week 44, no cases of rubella have been notified.

*Immunosurveillance*

During 2011, the results of the Pienter II project into the population's immunity against rubella will become available.

### *3.8.4 Pathogen*

For none of the nine reported cases could a genotype be determined. For most of the cases, notification was on basis of serological confirmation only and too late for successful RNA detection/sequencing. One positive rubella PCR determination was unsuccessful for genotyping. According to a new genotype standard as defined by WHO, this standard will be adopted by RIVM (2010/2011).

### *3.8.5 Adverse events*

See section 2.6.5.

### *3.8.6 Current/ongoing research*

See paragraph 3.7.6 regarding the mathematical modelling that is ongoing.

## 3.9 Meningococcal serogroup C disease

*S.C. de Greeff, W.A.M. Berbers, L.M. Schouls, J.M. Kemmeren*

### *3.9.1 Key points*

- Since the introduction of vaccination in the NIP, no cases of meningococcal group C disease in previously vaccinated persons have been reported.

### 3.9.2 *Changes in vaccine 2009-2010-2011*

There have been no changes in the composition or vaccination schedule for MenC and no changes are anticipated in the near future.

### 3.9.3 *Epidemiology*

Since the introduction of the conjugated MenC vaccine, the incidence of serogroup C disease has strongly decreased (Figure 9). In 2009, only nine cases of invasive meningococcal group C disease were reported. Two were unvaccinated children aged 8 months and 4 years, respectively. All other cases were in unvaccinated adults (Table 9).

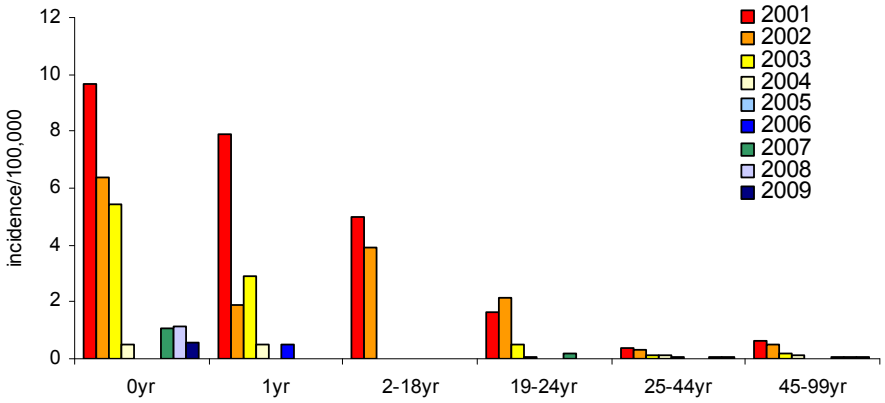



**Figure 9 Age-specific incidence of meningococcal C disease by year, 2001-2009**

**Table 9 Absolute number of patients with meningococcal C disease**

| Age (Yrs) | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 2 | 20 | 13 | 11 | 1 | 0 | 0 | 2 | 2 | 1 |
| 1 | 5 | 16 | 4 | 6 | 1 | 0 | 1 | 0 | 0 | 0 |
| 2-18 | 60 | 164 | 131 | 1 | 1 | 0 | 0 | 1 | 0 | 1 |
| 19-24 | 10 | 19 | 25 | 6 | 1 | 0 | 0 | 2 | 0 | 0 |
| 25-44 | 7 | 18 | 17 | 7 | 6 | 2 | 1 | 1 | 3 | 2 |
| 44-99 | 21 | 39 | 31 | 11 | 7 | 2 | 2 | 3 | 6 | 5 |
| **Total** | **105** | **276** | **221** | **42** | **17** | **4** | **4** | **9** | **11** | **9** |

*Immune surveillance*

The analysis of the nearly 8000 serum samples collected during the Pienter II study revealed a gradual increase in the persistence of MenC specific antibody levels with age in the immunised cohorts of the mass campaign, even five years after the single vaccination (see report 2009). Currently, the nature and quality of this humoral immune response is being examined (avidity,

subclass distribution) in order to find explanations for its long-term persistence. It is also important to explore how this immune response develops further after five years.

*Vaccine effectiveness*

Since the introduction of MenC vaccination in the Dutch NIP, no cases of meningococcal group C disease in previously vaccinated persons have been reported.

### *3.9.4 Pathogen*

No change in the composition of the MenC population circulating in the Netherlands has been observed.

### *3.9.5 Adverse events*

Studies on the reactogenicity of vaccination with a novel HibMenCY conjugate vaccine given before the age of 5 years showed that these vaccines had a comparable safety profile to licensed vaccines.[38-40] Furthermore, several clinical trials showed that the tolerability profile of MenACWY-CRM was generally similar to control vaccines in children aged <10 years.[37-39]

In February 2010, the MenACWY-CRM vaccine was approved by the FDA for active immunisation in people 11-55 years of age. In addition, two studies evaluated this vaccine when administered concomitantly or sequentially with other adolescent vaccines: combined tetanus, reduced diphtheria and acellular pertussis and human papillomavirus vaccine. Both studies showed that these adolescent vaccines could be administered concomitantly without causing increased reactogenicity [39, 40]

### *3.9.6 Current/ongoing research*

See immune surveillance

*International news*

During the 17th IPNC (international pathogenic *Neisseria* conference) several presentations emphasised the important role of the carrier protein in the polysaccharide-protein conjugate vaccines(CV). It has become evident that as the number of glycoconjugates (valences) and dosage of carrier proteins (CP) included in CVs increase, so does the likelihood of interference with the immune response to conjugated and/or co-administered antigens.[41]

The sero-epidemiological situation in the UK concerning the herd immunity for MenC and the prevalence of antibody levels in the large cohort of people vaccinated with MenC conjugate vaccine is similar to that of the Netherlands, despite the difference in vaccination schedules (primary series at 2 and 3 months with a booster at 12 months in the UK vs. a single vaccination at 14 months here). In the UK, a booster vaccination for adolescents is also considered to maintain the present herd immunity induced/obtained by the mass catch-up campaign. Other countries with a large catch-up campaign for MenC vaccination like Canada and Spain, had lower vaccination coverage and lacked good surveillance data.

## 3.10 Hepatitis B

*S.J.M. Hahné, F.D.H. Koedijk, H.J. Boot, J.M. Kemmeren*

### *3.10.1 Key points*

- Analyses of notification data suggest the decrease in the incidence of acute hepatitis B in the Netherlands since 2003 was sustained in 2009.
- Infections acquired through heterosexual contact outnumbered those acquired through male homosexual contact. There were no cases reported due to injecting drug use.
- In 2011, universal infant vaccination against HBV will be introduced.

### *3.10.2 Changes in vaccine 2009-2010-2011*

Based on a recommendation by the Health Council (GR), the minister of Public Health, Welfare and Sports decided in July 2010 to introduce universal vaccination against HBV before the end of 2011.[42] The GR's advice to include a programme to vaccinate adolescents in this was not followed. The HBV vaccination will consist of four doses of Infanrix hexa, replacing the Infanrix penta vaccine used currently. The HBV vaccination programme for children born to HBsAg positive mothers will not change. The vaccination programme for those children of whom one or both parents are born in a HBV endemic country, will be integrated into the universal vaccination programme.

### *3.10.3 Epidemiology*

In 2009, 201 cases of acute hepatitis B were notified, a decrease of 8% compared to 2008. The incidence of notification of acute hepatitis B in 2009 was 1.2/100,000 population (2008: 1.3/100,000); 1.9 among men and 0.5 among women.

The median age of infection was 41 years for men and 33 years for women ($p<0.05$). Sexual contact was the most frequently reported route of transmission. This concerned male homosexual contact in 27% of cases and heterosexual contact in 41%. In 23% of cases, the route of transmission was unknown. As in 2008, no cases of transmission through injecting drug use were notified in 2009.[43]

The incidence of acute hepatitis B has decreased since 2003 and is now back at the level documented during the 1990s (Figure 10).

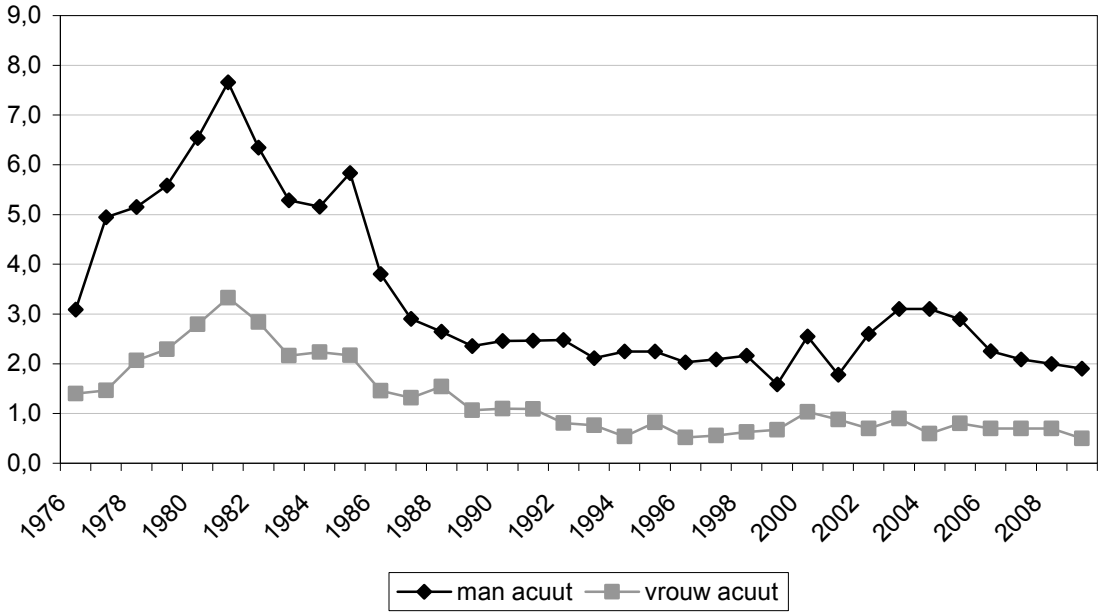



**Figure 10 Notifications of acute hepatitis B per 100,000 population by sex and year, The Netherlands, 1976-2009 (source: Osiris)**

*Immunosurveillance*

The results of the Pienter I and II projects concerning the population prevalence of (past) HBV infections in the general population have been determined. They will be reported in late 2010 after epidemiological analysis.

Steiner et al. assessed long-term immunity against HBV in children vaccinated during infancy with a hexavalent vaccine. At 4-5 years of age, 85.3% of subjects had persistent anti-HBs antibody concentrations ≥ 10 mIU/ml, rising to 98.6% after a HBV challenge dose.[44]

### *3.10.4 Pathogen*

No new data available

### *3.10.5 Adverse events*

Several studies were performed to evaluate the reactogenicity and safety of Hepatitis B vaccination with or without other childhood vaccines.[45-50] Suárez showed that with the combination vaccine DTPw-HepB-Hib, considerably fewer solicited local and systemic adverse events, such as fever and irritability, were found than with the comparator vaccines DTPw and Hib in healthy toddlers.[51] Furthermore, Dhillon concluded in a review that Infarix hexa as primary and booster vaccination was safe for all its component toxoids/antigens in infants aged <2 years, regardless of vaccination schedules. Its safety profile was generally similar to those of currently available vaccines, the diphtheria, tetanus and acellular pertussis-based pentavalent vaccines plus monovalent HBV or Hib vaccines.[52] Hepatitis B vaccines in healthy adolescents and adults also are considered to be mild or moderate severe.[53-56]

### 3.10.6 *Current/ongoing research*

No large research projects regarding HBV are planned for 2011.

## 3.11 Pneumococcal disease

*S.C. de Greeff, L.M. Schouls, J.M. Kemmeren*

### 3.11.1 *Key points*

- The introduction of vaccination against pneumococcal disease in the National Immunisation Programme has led to a considerable reduction in the number of cases of invasive pneumococcal disease (IPD) caused by the vaccine serotypes in the vaccinated cohorts.
- A reduction in vaccine type IPD has also been observed in other age groups, although this reduction has been partly counterbalanced by an increase in non-vaccine type IPD

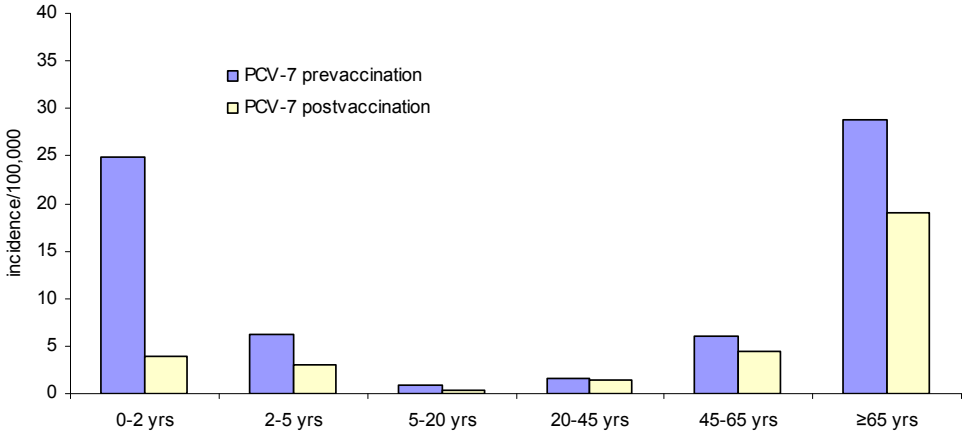
### 3.11.2 *Changes in vaccine 2009-2010-2011*

There have been no changes in the composition or vaccination schedule for pneumococci in 2009. In 2011 a new 10-valent vaccine (Synflorix, GSK) will replace the currently used 7-valent vaccine (Prevenar, Pfizer) in the Netherlands.

### 3.11.3 *Epidemiology*

*Disease*

Since 2009 IPD has become a notifiable disease for children up to 5 years of age. For a description of epidemiological trends in the whole population, we rely on laboratory surveillance data of the Netherlands Reference laboratory for Bacterial Meningitis (NRBM). This system covers about 80% of all cases of pneumococcal meningitis in the Netherlands. Data for other pneumococcal disease manifestations (pneumonia and sepsis) are only complete for nine sentinel labs, covering about 25% of the total population in the Netherlands. Unless otherwise stated, the numbers below reported by the nine sentinel labs are extrapolated for the whole population (i.e., multiplied by 4).



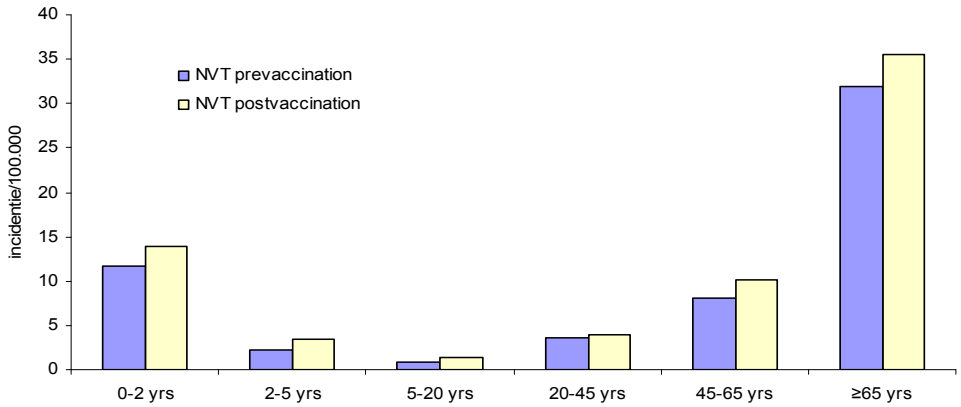



**Figure 11 Age-specific incidence of vaccine type IPD (upper figure) and non-vaccine type IPD (lower figure), in blue before introduction of vaccination (June 2004-June 2006) and in yellow in the post-vaccination period (June 2006-Oct 2010). Incidences are calculated on cases reported by the nine sentinel labs, but extrapolated for the whole population**

Vaccine-type IPD decreased by 84% in children <2 years of age. A reduction of vaccine type IPD has also been observed in other age groups (Figure 11). However, this reduction has been partly counterbalanced by an increase in non-vaccine type IPD (Figure 11). The overall incidence in IPD in the 0-2, 2-5, and ≥65 yrs age groups decreased by 51% (p<0.0001), 23% (p=0.04) and 10% (p<0.0001), respectively. In the 5-20 yrs and 45-65 yrs age groups, the incidence remained stable, while in the 20-45 yrs age group, a 5% increase was observed (p=0.31).

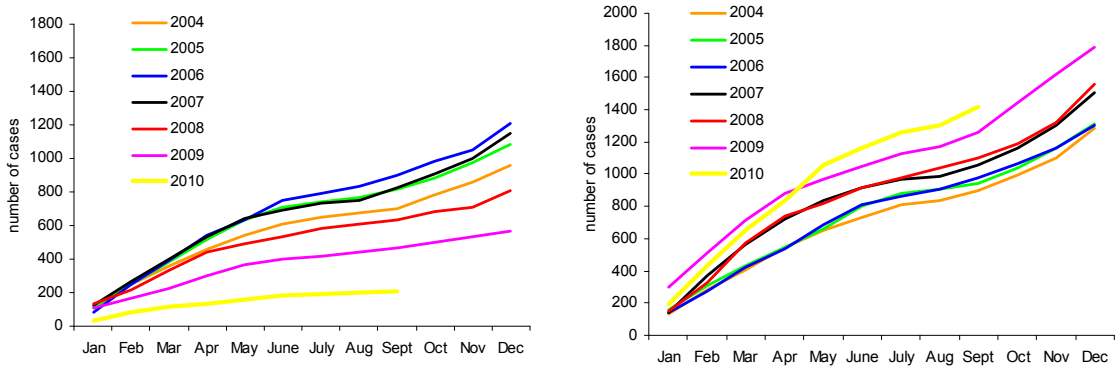



**Figure 12 Cumulative number of vaccine-type IPD (left) and non-vaccine type IPD (right) per year in patients older than 2 years of age.**

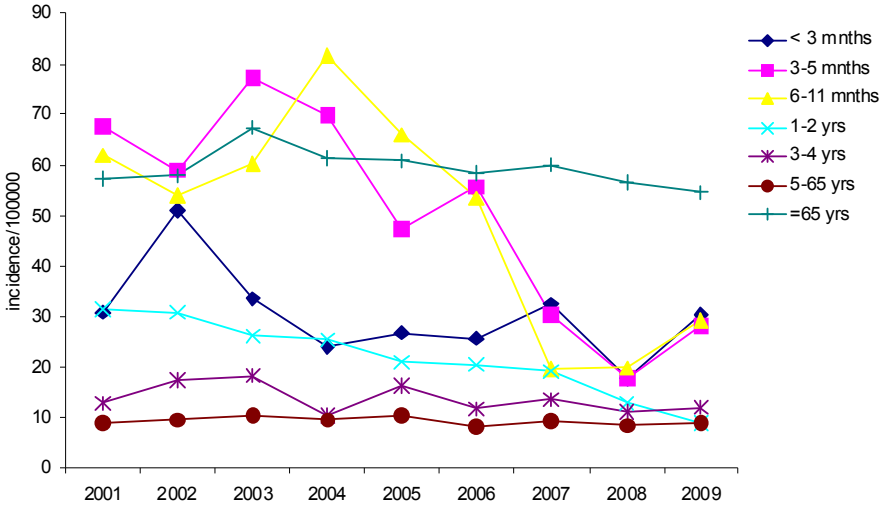



**Figure 13 Age-specific incidence of hospitalisation due to pneumococcal disease ( i.e., ICD9 codes 3201 (pneumococcal meningitis), 0382 (pneumococcal septicemiae), 481 (pneumococcal pneumoniae) and 4823 (pneumoniae by Streptococcus)**

Based on discharge diagnoses as registered in the National Medical Register, the incidence of hospital admission because of meningitis, sepsis and pneumoniae caused by pneumococci – i.e., ICD9 codes 3201 (pneumococcal meningitis), 0382 (pneumococcal septicemiae), 481 (pneumococcal pneumoniae) and 4823 (pneumoniae by *Streptococcus*) – decreased in the age groups targeted for vaccination since 2006 (children from aged 3 months – 2 years). (Figure 13)

*Immune surveillance*

The nearly 8000 serum samples collected during the Pienter II study were analysed in a serological assay that simultaneously measures the antibody concentrations against the 13 different pneumococcal serotypes, targeted with the 13 valent conjugate vaccine.[57] In contrast to most other analyses of the Pienter sera, this study assesses the prevalence of antibodies induced after natural exposure to the pneumococci. It does not measure the vaccine induced antibodies. This study therefore is to be regarded as an assessment of the seroprevalence before the introduction of the pneumococcal vaccine. The geometric mean IgG concentrations (GMCs) against the 13 serotypes in unvaccinated individuals increased with age up to 5 years and remained at a plateau thereafter. Furthermore, individuals develop antibodies against an increasing number of different serotypes with increasing age. There was no uniform relationship between the occurrence of serotypes causing invasive pneumococcal disease (IPD) and the GMCs against these serotypes.

*Vaccine effectiveness*

Up to October 2010, eight vaccinated children have been reported with vaccine type IPD (Table 10).

**Table 10 Children that have been reported with vaccine type IPD**

| Year of diagnosis | age (months) | serotype | Number of vaccinations received | Patient details |
|---|---|---|---|---|
| 2006 | 4 | 18C | 1 | premature |
| 2007 | 2 | 23F | 1 | - |
| 2008 | 3 | 6B | 2 | - |
| 2008 | 3 | 9V | 2 | diagnosis within 1 wk after 2nd dose |
| 2008 | 7 | 6B | 3 | - |
| 2009 | 29 | 19F | 4 | - |
| 2009 | 6 | 19F | 3 | deceased |
| 2010 | 12 | 6B | 4 | - |

### 3.11.4 *Pathogen*

As mentioned above, there are gradual shifts in the composition of the pneumococcal population at the serotype level. Currently, isolates are analysed using genotyping methods to study the impact of the vaccination on the currently circulating pneumococci.

### 3.11.5 *Adverse events*

Several studies were conducted which compared the safety of PCV13 with PCV7 vaccines. All studies concluded that the safety and tolerability of both vaccines were comparable, and reactogenicity was in general mild.[58-61] Furthermore, Veskari et al. found that a booster dose of the 10-valent pneumococcal non-typeable *Haemophilus influenza* protein D conjugate vaccine and MMRV vaccine can be co-administered without compromising the safety profiles of either vaccine.[62]

In a phase 2 study to find an optimal vaccination strategy (i.e., 0, 1, 2, or 3 PCV-7 doses with or without the 23-valent pneumococcal polysaccharide vaccine (PPV-23) at 12 months), showed that the PPV-23 vaccine was well tolerated.[63] Following PPV-23 at 12 months of age, low-grade fever was common (28.2%) while high-grade fever occurred in 6.1%. Local injection site reactions occurred in a minority of recipients.

### 3.11.6 *Current/ongoing research*

Ongoing research in the RIVM has already demonstrated variation in the composition of the genes that encode the capsular polysaccharide of serogroup 6 and 19 pneumococcal strains isolated from patients with invasive pneumococcal disease. Currently, the consequences of these genetic changes for the antigenic properties and the level of expression of the capsular polysaccharides are under investigation. Several clinical studies have been performed or are ongoing. The Minoes study looked at the effect of a reduced dose schedule of Prevnar-7 on

immunogenicity and carriage before introduction in NIP (Van Gils et al., 2009, 2010; Rodenburg et al., 2010). The Kokki study was carried out to study the induction of memory after vaccination with Prevnar-7. The Okidoki study looking at the effect of vaccination on carriage two years after introduction of Prevnar in NIP is ongoing (Spijkerman et al., accepted). A PIM study has started to study the effect of vaccination schedules on the immunogenicity of Prevnar-13.

## 3.12 Human papillomavirus (HPV) infection

*C.C.H. Wielders, M.C.W. Feltkamp, H.J. Boot, M. Mollers, T.M. van 't Klooster, J.M. Kemmeren, N.A.T. van der Maas, E.A. van Lier, H.J. Vriend, M.A.B. van der Sande, J.A. Bogaards, H.E. de Melker*

### *3.12.1 Key points*

Uptake

- In 2010, vaccination coverage for the first and second dose in the first NIP cohort, i.e., girls born in 1997, was 56% and 53%, respectively. The coverage for three doses among girls of the catch-up campaign increased from 45% to 47% in 2010.
- Risk factors for a lower uptake of at least one vaccination among girls born in 1997 were as follows; both parents not born in the Netherlands, living in one of the four biggest cities of the Netherlands, living in areas with a low socioeconomic status and girls living in municipalities with ≥15% of the people voting for the Reformed Political Party (SGP).
- A recent modelling study observed that the cost-effectiveness of HPV vaccination in the Netherlands is not negatively affected by the unexpectedly low vaccination uptake, especially if herd immunity is taken into account.

Adverse events

- The report rate for spontaneous reported adverse events after the HPV catch-up campaign in 2009 was 11.6 per 10,000 administered doses. No Severe Adverse Events (SAE) with assessed causality were reported.
- The report rate of presyncope and syncope after the HPV catch-up campaign in 2009 was 16.8 per 10,000 administered doses.
- Local reactions (such as pain at the injection site) and systemic events (such as mylagia, fatigue and headache) were reported in ~83-85% of the girls after the HPV catch-up campaign.

Research

- HPV seropositivity increases significantly with age, starting at the age of 16 years. A former diagnosis of a sexually transmitted disease is significantly associated with HPV seropositivity.

- VE against cervical intraepithelial neoplasia 2+ (CIN2+), associated with HPV16/18 is high (above 90% after approximately three years of follow-up). The vaccine also protects against CIN2+ caused by non-vaccine oncogenic HPV types (cross-protection).

### *3.12.2 Changes in 2009-2010-2011*

In the Netherlands, the bivalent vaccine Cervarix® (GlaxoSmithKline) is used in the Dutch NIP, which protects against infection with HPV types 16 and 18. A second vaccine is also available, Gardasil® (Merck & Co.), which prevents against infection with HPV types 6/11/16/18. Both vaccines are administered in three doses (Cervarix® vaccination scheme: month 0, 1, 6; Gardasil® vaccination scheme: month 0, 2, 6).

The first regular NIP HPV vaccination campaign started in April 2010, targeting 12-year-old girls (i.e., birth cohort 1997). The vaccination coverage in the catch-up campaign in 2009 for girls born in 1993-1996 was 50%, 49% and 45% for first, second and third dose, respectively. Girls born in 1993-1996, who did not attend the catch-up vaccination campaign in 2009, were offered a second opportunity to for vaccination in 2010. Up to June 29, 2010, the coverage of three doses among girls in the catch-up campaign has increased to 47%; of the girls from the 1997 birth cohort, 53% has received two vaccinations, as results from the third dose were not yet available.[64]

When different background characteristics of girls born in 1997 were investigated, significant differences in uptake of at least one dose of the vaccine were observed. Girls of whom both parents were not born in the Netherlands showed a lower coverage than girls of whom both parents were born in the Netherlands (31.7% versus 60.1%, respectively), although country of birth of the parents was only known for 17% of the girls. Furthermore, girls who live in one of the four biggest cities in the Netherlands (G4: Amsterdam, the Hague, Rotterdam, Utrecht) had a lower uptake for at least one vaccination (45.4%) than girls living in other cities (G32: a network of 32 cities in the Netherlands without the G4 cities) (56.6%) or other municipalities (60.0%). Postal code areas with a low socioeconomic status also showed a lower uptake for at least one vaccination compared to postal code areas with a high socioeconomic status (46.2% versus 63.9%). Finally, in municipalities with a high percentage of Reformed Political Party (SGP) voters during the elections of the House of Representatives (Tweede Kamer) in 2010, fewer girls were vaccinated at least once compared to municipalities with a low percentage (≤4%) of SGP voters (34.2% versus 59.2%).

In addition, a preliminary analysis of late adopters ("spijtoptants", a girl who did not start with the vaccination initially but started later on in the campaign) and dropout girls ("uitvallers", a girl who started initially but did not complete the series of three vaccinations), born in 1993-1996, was carried out. Background characteristics of these girls were compared to characteristics of girls who completed the three dose scheme in 2009 according to the regular

programme in the region of their hometown (regular). Two categories of late adopters were defined; one group that started later on in 2009, but not on their first opportunity (late adopter 2009) and a group that started vaccinating in 2010 instead of 2009 (late adopter 2010). Of the birth cohorts 1993-1996, 41.8% was vaccinated regularly, 1.1% was a late adopter 2009, 6.3% was a late adopter 2010 and 3.7% was a dropout. Great differences in distributions between these categories were observed in the Municipal Health Service (GGD) regions. Dropout girls and late adopters in 2009 showed similar background characteristics, while late adopters in 2010 had background characteristics which were comparable to the girls who completed the scheme regularly. Among late adopters in 2009 and dropout girls, relatively more girls had parents who were not born in the Netherlands, were living in one of the four biggest cities or lived in postal code areas with a low socioeconomic status compared to late adopters in 2010 and regularly vaccinated girls. This analysis will be repeated in 2011, when the 1997 birth cohort has had the opportunity to receive three vaccinations.

### *3.12.3 Epidemiology*

#### 3.12.3.1 Immune surveillance data

Data on routine immune surveillance are not available, however in 2010, two studies have been published on the baseline seroprevalence of HPV types in the Netherlands.[65, 66] The first study, conducted by Kramer et al., investigated 637 cross-sectional sera of 11-26-year--old Dutch females on the presence of HPV types 6/11/16/18 antibodies (samples from PIENTER 2 project). They found an overall seroprevalence of 7.9%. Antibodies against HPV types 6/11 were found in 4.3% of the sera. Antibodies against HPV16/18 were detected in 4.4% of the samples. They also found a significant increase in HPV seropositivity with age (OR 1.2; 95% CI 1.1-1.4), starting at the age of 16 years. A former diagnosis of a sexually transmitted disease was significantly associated with HPV seropositivity (OR 6.3; 95% CI 2.2-17.9).[65]

The second study, conducted by Heiligenberg et al., was performed to determine differences in the seroprevalence of eight high-risk human papillomavirus (hrHPV) types among men having sex with men (MSM), heterosexual men and women in the general population of Amsterdam. Sera of 1349 inhabitants aged 17 years or older were tested for the presence of antibodies against L1 capsid proteins of eight hrHPV types (types 16/18/31/33/35/52/58/45). The seroprevalences for the eight hrHPV types ranged from 13.1% for HPV45 to 31.4% for HPV35. Seropositivity for HPV16 and HPV18 was more common in women and MSM than in heterosexual men. HPV16 and HPV18 were more common in subjects also having antibodies against other hrHPV types (prevalence rate ratio (PRR), 2.12, 95% confidence interval (CI) 1.52-2.97; and PRR, 2.00; 95% CI, 1.43-2.81, respectively) and/or herpes simplex virus type 2 (PRR 1.69; 95% CI 1.32-2.16; and PRR 1.47; 95% CI 1.13-1.92, respectively). HPV18 was more common in persons with a history of sexually transmitted infections (STI) (PRR 1.64; 95% CI 1.20-2.25). HPV types 35/45/58 were more common in non-European ethnic groups.[66]

A comment on the use of serology to detect HPV is that not all HPV infections result in seroconversion.[67, 68] The maximum seroconversion rate of IgG after incident HPV16 infection was 56.7% by eight months in a study by Ho et al. among young female students (mean age 20 years).[67] A study by Carter et al. observed seropositivity 18 months after incident HPV6, HPV16 or HPV18 infection in about 60% of the women.[68] Despite incomplete seroconversion and waning of antibodies, population-based sero-epidemiological studies performed before and at regular intervals after introduction of vaccination is one of the tools to monitor the impact of mass vaccination against HPV on the frequency of HPV infection.

#### 3.12.3.2 Vaccine effectiveness

The long-term efficacy of both HPV vaccines, Cervarix® and Gardasil®, is still under investigation. Several studies have reported the efficacy of the vaccine against intermediate end-points (e.g., CIN2+) a few years after administration. The final results of a phase III randomised, double-blind, controlled study of Cervarix® (PATRICIA)[69] were published in 2009.[70] After a mean follow-up of 34.9 months (women aged 15-25 years), the VE against CIN2+ associated with HPV16/18 in the per-protocol population was 92.9% (96.1% CI 79.9-98.3), and 98.1% (96.1% CI 88.4-100) in an analysis in which probable causality to HPV type was assigned to lesions infected with multiple oncogenic types. A 100% efficacy (96.1% CI 36.4-100) was found against CIN3+ associated with HPV16/18, and a 53% reduction in CIN2+ associated with HPV31/33/45/52/58 (cross-protection of the HPV16/18 vaccine). They concluded that HPV16/18 AS04-adjuvanted vaccine (Cervarix®) showed high efficacy against CIN2+ associated with HPV16/18 and some non-vaccine oncogenic HPV types (31/33/35/39/45/51/52/56/58/59/66/68) and a substantial overall effect in cohorts that are relevant to universal mass vaccination and catch-up programmes.[70] A study from Brazil (7.3 years of follow-up, vaccine: N=190, placebo: N=167) found a Cervarix® vaccine efficacy of 94.5% (95% CI 82.9-98.9) for incident infection, 100% (95 CI 55.7-100) for 12-month persistent infection and 100% (95% CI -129.8-100) for CIN2+.[71]

Regarding the efficacy of Gardasil®, Kjaer et al. published a pooled analysis of three clinical trials [72-74] which included 18,174 females aged from 16-26 years old with a mean follow-up time of 42 months.[75] VE against HPV6/11/16/18-related high-grade cervical lesions (CIN2+ or worse) in the per-protocol and intention-to-treat populations was 98.2% (95% CI 93.3-99.8) and 51.5% (95% CI 40.6-60.6), respectively. VE against HPV6/11/16/18–related high-grade vulvar and vaginal lesions in the per-protocol and intention-to-treat populations was 100.0% (95% CI 82.6-100.0) and 79.0% (95% CI 56.4-91.0), respectively. Additionally, the FUTURE I/II Study Group published a four-year efficacy study on Gardasil® (42 months follow-up).[76] They found a VE of the per-protocol population of 96% for cervical intraepithelial neoplasia grade 1 (95% CI 91-98), 100% for both vulvar and vaginal intraepithelial neoplasia grade 1

(95% CI 74-100, 64-100 respectively), and 99% efficacy against genital warts (95% CI 96-100).

To predict the long-term duration of immunity, immunogenicity data can be useful. David et al., found that there was no evidence of further decline from three years to six years after an initial drop from the peak antibody titres at month seven, which suggests that mean antibody concentrations should remain well above those associated with natural infection in the near future (and for ≥20 years according to the results of a statistical model).[77] Additionally, Einstein et al. compared the immunogenicity of Cervarix® and Gardasil®. Cervarix® was found to induce higher levels of neutralising antibody in serum and cervicovaginal secretions and of circulating antigen-specific memory B-cells and T-cells directed at HPV16 and HPV18 strains, compared with Gardasil®.[78]

#### 3.12.3.3 HPV related cancers

Between 2000 and 2008, every year 600 to 700 women were diagnosed with cervical cancer (Table 11). [79] Over the past 10 years, on average 221 fatal cases of cervical cancer were reported per year (Table 12).[79, 80] Apart from cervical cancer, other cancers related to HPV infections include cancer of the vagina, vulva, penis, anus, mouth and (oro)pharynx. HPVs are estimated to cause 90-93% of anal cancer, 40-64% of vaginal cancers, 40-51% of vulvar cancers, 36-40% of penile cancers[81], 40-64% of oropharyngeal cancers[82, 83] and at least 3% of oral cancers [84]. Table 8 shows the number of men and women who were diagnosed with these types of cancer in 2000-2008. The number of men and women who died in 2000-2009 from these types of cancer is shown in Table 12.

#### 3.12.3.4 Genital warts

In 2009, 2,729 diagnoses of genital warts (2.9% of all STI centre consultations in 2009) were reported in the national surveillance of STI centres, compared to 2,465 diagnoses in 2008 (2.8% of all STI centre consultations in 2008) (both percentages are probably an underestimation). For general practitioners, the number of reported diagnoses was estimated at 22,559 (95% CI 17,432-29,780) in 2008. An increase in the reporting rate for genital warts was also found for diagnoses by GPs: among women the reporting rate was 135 per 100,000 in 2008 compared to 113 per 100,000 in 2007, and the reporting rate for men increased even more, from 91 per 100,000 in 2007 to 140 per 100,000 in 2008. Most diagnoses were made in women aged 20-24 years and this is in line with previous years. The second most diagnoses were made in heterosexual men aged 25-29 years, while in 2007 most diagnoses were made among the 20-24 years of age category. The most frequently diagnosed co-infection was *Chlamydia*, which was found in 10.3% of cases with genital warts (in 12.6% of men who have sex with men, 11.6% of female cases with genital warts, and 8.0% of heterosexual male cases).[85]

Genital warts are caused by HPV6 or HPV11, types that are not included in the Dutch immunisation programme. In some other countries, such as the USA and Australia, however, these types are included in the immunisation programme. Current studies in Australia have shown a remarkable reduction of the incidence of genital warts in the vaccinated population, as well as in unvaccinated men who have sex with women.[86-88] This reduction might also provide protective effects in heterosexual men through herd immunity.[89] Donovan et al. also speculated about the population benefit of the quadrivalent HPV vaccine, which would be a widespread reduction in infections and disease caused by HPV16 and HPV18. This reduction might already be underway, but it will take longer to confirm than the observation of decreased incidence of genital warts.[89]

### *3.12.4 Pathogen*

Since the HPV16/18 vaccination has been introduced in pre-adolescent girls, awareness is needed for possible changes in HPV genotype distribution (e.g., replacement for other, potentially, high-risk HPV types not included in the vaccine) and changes in the antigenicity of the circulating HPV16/18 genotypes. The likelihood of these events occurring is considered low, as HPV is a stable DNA virus. Nevertheless, to detect these changes it is essential to obtain baseline HPV genotype diversity patterns prior to vaccination. Detailed molecular analyses, nested in the HPV vaccine cohort study and the HPV STI study (see Current/Ongoing Research) will show if HPV types possibly drift (changes in the amino acid sequence of the HPV16/18 L1 and L2 capsid proteins) or shift (replacement of HPV16/18 by other potentially high-risk HPV types). Because HPV vaccination was introduced rather late in the Netherlands compared to other developed countries, it is expected that the first indications in this regard will be detected abroad.

So far, one Finnish study showed an increased risk to seroconvert for another HPV type (type 33) in unvaccinated women with HPV16 and HPV18 antibodies compared to women with no antibodies on baseline. These findings suggest a possible competitive advantage for HPV33 over other genital HPV types in the unvaccinated population, since no comparable, consistent patterns by baseline HPV16 or HPV18 serostatus were observed for the other hrHPV types.[90] Apart from this study, no other clear signs of replacement or antigenic shift have been reported in the literature. A drift is also not expected because of the fact that HPV replicates using cellular DNA polymerases and thus, has a slow mutation rate.[91]

To be able to detect changes in the prevalence of different HPV types, baseline prevalence of the period before vaccination is necessary. So far, two Dutch studies have been published on cross-sectional baseline HPV prevalence based on viral DNA detection.[92, 93] Lenselink et al., genotyped samples of 2065 women aged 18-29 years and found an HPV point prevalence of 19%, a low-risk HPV prevalence of 9.1%, and a high-risk HPV prevalence of 11.8%. HPV16 was present in 2.8% of the women, type 18 in 1.4%. Coupé et al. determined the prevalence of

45,362 samples of women aged 18-65 years old. The overall high-risk HPV prevalence was 5.6% and peaked at the age of 22, with a prevalence of 24%. HPV type 16 was the most common, in 1.8% of all women. Finally, the high-risk prevalence in all women aged 29-61 years old decreased significantly with age for all high-risk HPV types.[93] Data from these studies will be completed in the near future with new epidemiological baseline data from a Dutch cohort of 13-16 year old girls prior to vaccination and data from a cross-sectional study in female and male STI clinic visitors aged 16-24 years old (see Current/Ongoing Research).

### *3.12.5 Adverse events*

3.12.5.1 National data:

During the 2009 catch-up campaign for 13-16 year old girls, RIVM received 647 spontaneous reports of adverse events, resulting in a reporting rate of 11.6 per 10,000 administered doses.[94] The number of so-called major events was 87 (13.4%) and minor events accounted for 86.6% (n=560). In 28.4% (n=184) of the reports no medical help was sought or was not recorded by us. Paracetamol and other home medication was administered in 16.1% (n=104). In 30.6% (n=198) a GP was contacted (contact rate of 3.6 per 10,000 administered doses). In 6.6% (n=43) of the reports, the girls went to a hospital (contact rate of 0.8 per 10,000). No SAE with assessed causality were reported.[94]

Surveillance of immediately occurring adverse events during mass vaccination aimed to monitor the occurrence of presyncope, syncope and anaphylaxis. The incidence of presyncope and syncope was 16.8 per 10,000 administered doses. No anaphylactic shock was reported. GP contact rate and intervention of ambulance personnel was 0.29 and 0.22 per 10,000 administered doses, respectively.[94]

A questionnaire study on adverse events occurring within one week after vaccination was performed during the catch-up campaign in 2009 on six vaccination locations in the central part of the Netherlands.[94, 95] One or more questionnaires were returned by 4248 of the 5950 girls who agreed to participate; 68.7% returned the questionnaire after the first vaccination, 47.4% after the second vaccination and 50% after the third vaccination. Local reactions occurred in 92.1%, 79.4% and 83.3% of the girls respectively, after the three successive vaccinations. Pain and reduced use of the arm were the most reported local reactions. The occurrence of systemic events was reported in 91.7%, 78.7% and 78.4% after the three successive vaccinations. Myalgia, headache and fatigue were most frequently reported. Medical intervention was required for 1.2% of the girls within one week after vaccination. Two of them visited a medical specialist; a causal association with the vaccination was possible in one of them. Four girls visited the emergency care within one week after vaccination; a causal relation with the vaccination was possible only in one case. However, no serious or unexpected adverse events were reported with a known causal relation to the vaccination. Our findings of high

proportions of adverse events, which were mostly mild, were comparable to other studies.[69, 70, 96-100]

3.12.5.2 International data

A pooled analysis of the safety of Cervarix® has been published.[101] Almost 30,000 girls and women aged 10 years or older participated in the cohort (16,142 who received at least one dose of HPV16/18 vaccine and 13,811 who received a control vaccine). Rates of solicited local and general symptoms were higher in the HPV16/18 vaccine group than in the control groups. No clinically relevant differences were observed between the HPV16/18 vaccine and pooled control groups in rates of SAEs (2.8% versus 3.1%), medically significant conditions (19.4% versus 21.4%), new onset of chronic diseases (1.7% in both groups) or new onset of autoimmune diseases (0.4% versus 0.3%). Furthermore, no differences in pregnancy outcomes or rates of withdrawals due to adverse events (AEs) or SAEs were observed between groups. Similar results were found in two other studies, which were not included in the pooled analysis.[102]

In the UK, a surveillance system (Yellow Card Scheme) was set up to monitor adverse events of the Cervarix® vaccination.[103] From April 2008 up to the end of July 2010, the Medicines and Healthcare products Regulatory Agency (MHRA) had received 4703 Yellow Cards (10.5 reports per 10,000 administered doses) in association with the Cervarix® vaccine. The vast majority of suspected adverse reactions reported to MHRA in association with the bivalent vaccine was related to either the signs and symptoms of recognised side effects or to the infection process and not the vaccine itself (i.e., 'psychogenic' in nature such as faints). They concluded that the balance of risks and benefits of the bivalent HPV vaccine remains positive following administration of at least 4 million doses.[104]

For the quadrivalent vaccine Gardasil®, Slade et al. performed a post licensure safety investigation with data from the US Vaccine Adverse Event Reporting System (VAERS). VAERS registers AEFI. A rate of 53.9 reports per 100,000 doses distributed was found. A total of 772 reports (6.2% of all reports) described serious AEFIs, including 32 reports of death. Most of the AEFI rates were not greater than the background rates compared with other vaccines but there was disproportional reporting of syncope and venous thrombo-embolic events, although this can be a result of a passive reporting system instead of a disproportionate event caused by the vaccine.[105]

A study by Einstein et al. compared adverse events between Cervarix® and Gardasil® and found that both vaccines were generally well tolerated and that the incidence of unsolicited adverse events was comparable between vaccinated groups. Furthermore, the incidence of solicited symptoms was generally higher after Cervarix®, with injection site reactions being most common.[78]

### *3.12.6 Current/Ongoing research*

#### 3.12.6.1 HPV prevalence

Currently, three studies are being performed to gain more insight into the prevalence of current HPV infections in the Netherlands. The first study is a five-year prospective cohort study among 15-16-year-old vaccinated and unvaccinated girls, which was initiated in 2009. The first baseline results are currently being analysed. Secondly, a cross-sectional study on the occurrence of HPV infections (HPV16/18/others) in female and male STI clinic visitors, aged 16-24 years old, also started in 2009 (baseline, before start of vaccination campaign). These data are currently being analysed. The study will be repeated once every two years (new data will be collected in early 2011). This repeated measurement design gives an opportunity to detect shifts or replacements of HPV types as a result of the vaccination campaign. Finally, 5000 samples collected from women aged 16-29 years in the *Chlamydia* Screening Implementation (CSI) study are being analysed for the presence of different HPV genotypes.[106, 107] Results of this study will become available in 2011.

#### 3.12.6.2 Modelling

The long-term impact of HPV vaccination in the Netherlands is being explored by mathematical models. A type-specific transmission model has been calibrated to match pre-vaccine data on HPV DNA prevalence, viral clearance and progression up to high-grade cervical lesions.[108] On the basis of this model, changes in the forces of infection for specific HPV types can be calculated as a function of age and time since the introduction of a vaccination programme. These forces of infection have been used as input in a micro-simulation model for cervical carcinogenesis to predict the impact of HPV vaccination on rates of cervical abnormalities, screening outcomes and the incidence of cervical cancer. It appears that elimination of HPV vaccine types is unlikely due to their high transmissibility but it can be expected that vaccination induces substantial protective effects in non-vaccinated men and women as a result of reduced transmission of HPV vaccine types. Specifically, the number of cancer cases averted among non-vaccinees is predicted to be highest at between 50-70% vaccine coverage, with one in four cervical cancer cases prevented among non-vaccinated women.[109]

The cost-effectiveness of HPV vaccination has so far not been negatively affected by the unexpectedly low vaccine uptake. Due to the high cost of the HPV vaccine (125 euros per dose at the current pharmacy price), the total cost of vaccination scales more or less linearly with vaccine uptake. If indirect protective effects (i.e., herd immunity) of HPV vaccination are neglected, its effectiveness also scales linearly with vaccine uptake. Consequently, the Incremental Cost-Effectiveness Ratio (ICER) would change from ~19 500 euros per Quality-Adjusted Life-Year (QALY) at 85% coverage – the anticipated scenario as outlined in the Health Council (Gezondheidsraad) report – to ~20 600 euros per QALY at the realised scenario in 2009-2010 (simplified as yielding 50% coverage). However, if herd immunity is taken into

account, the overall effectiveness of HPV vaccination decreases less than its associated cost and the ICER decreases to ~15 000 euros per QALY.

Research on the efficiency and cost-effectiveness of including boys in the vaccination programme is ongoing. Inclusion of endpoints other than cervical cancer is also under investigation. In addition, a PhD project has been initiated to predict the impact of the HPV vaccination campaign on the future incidence of cervical cancer from intermediate endpoints and to identify surrogate population-based endpoints that are informative for assessing the extent of herd immunity obtained through HPV vaccination.

**Table 11 Number of new ano-genital, mouth, pharynx, and cervical cancer cases in the Netherlands from 2000-2008, by cancer type (The Netherlands Cancer Registry (NKR))**

| Sex | Cancer type | | '00 | '01 | '02 | '03 | '04 | '05 | '06 | '07 | '08 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Men | Ano-genital | - Penis (C60) | 77 | 93 | 103 | 104 | 117 | 110 | 118 | 113 | 128 |
| | | - Anus (C21) | 49 | 49 | 50 | 65 | 51 | 52 | 66 | 60 | 77 |
| | Mouth (C01-06) | | 471 | 471 | 460 | 500 | 532 | 541 | 502 | 491 | 554 |
| | Pharynx (C09-14) | | 378 | 378 | 369 | 384 | 404 | 394 | 401 | 379 | 472 |
| Women | Cervix (C53) | | 686 | 604 | 650 | 606 | 708 | 682 | 686 | 737 | 699 |
| | Ano-genital | - Vulva/vagina (C51-52) | 278 | 291 | 292 | 317 | 307 | 323 | 341 | 376 | 361 |
| | | - Anus (C21) | 64 | 76 | 60 | 70 | 59 | 79 | 86 | 80 | 84 |
| | Mouth (C01-06) | | 324 | 345 | 322 | 351 | 344 | 363 | 372 | 401 | 365 |
| | Pharynx (C09-14) | | 127 | 155 | 155 | 143 | 156 | 139 | 162 | 170 | 161 |

**Table 12 Number of deaths related to ano-genital, mouth, oropharynx, pharynx, and cervical cancer cases in the Netherlands from 2000-2009, by cancer type.[79, 80]**

| Sex | Cancer type | | '00 | '01 | '02 | '03 | '04 | '05 | '06 | '07 | '08 | '09 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Men | Ano-genital | - Penis (C60) | 20 | 23 | 13 | 20 | 23 | 21 | 14 | 31 | 26 | 24 |
| | | - Anus (C21) | 11 | 18 | 15 | 12 | 11 | 19 | 11 | 16 | 17 | 21 |
| | Mouth (C01-06) | | 133 | 129 | 119 | 140 | 136 | 148 | 137 | 145 | 145 | 155 |
| | Oropharynx (C09-10) | | 70 | 69 | 65 | 73 | 77 | 63 | 73 | 66 | 64 | 66 |
| | Pharynx (C09-14)* | | 190 | 189 | 196 | 194 | 192 | 163 | 208 | 176 | 195 | 212 |
| Women | Cervix (C53) | | 258 | 243 | 187 | 214 | 203 | 235 | 214 | 204 | 244 | 209 |
| | Ano-genital | - Vulva/vagina (C51-52) | 108 | 101 | 111 | 118 | 98 | 106 | 114 | 101 | 118 | 128 |
| | | - Anus (C21) | 15 | 16 | 17 | 10 | 13 | 19 | 15 | 10 | 16 | 18 |
| | Mouth (C01-06) | | 90 | 87 | 89 | 114 | 102 | 86 | 94 | 94 | 90 | 113 |
| | Oropharynx (C09-10) | | 19 | 26 | 37 | 37 | 34 | 24 | 24 | 28 | 30 | 38 |
| | Pharynx (C09-14)* | | 55 | 63 | 88 | 73 | 97 | 76 | 67 | 74 | 71 | 83 |

* Number of deaths due to pharynx cancer includes the numbers of oropharynx cancer deaths as well

# 4 Future NIP candidates

## 4.1 Rotavirus infection

*I.H.M. Friesema, W. van Pelt and J.M. Kemmeren*

### *4.1.1 Key points*

- The incidence of rotavirus associated gastroenteritis appears to be rising.
- Rotavirus is the most important cause in case of hospitalisation due to gastroenteritis in children aged younger than 5 years.
- In a recent Dutch study, 1 in 5 adults hospitalised with gastroenteritis had a rotavirus infection.
- In the Netherlands, serotype G1[P8] is the most common type.

### *4.1.2 Changes in vaccine*

-

### *4.1.3 Epidemiology*

The Working Group Clinical Virology reports the number of rotavirus positive results weekly.[110] In 2006, this number was much higher compared to the years before. After a drop in 2007, numbers continued to be high. With the use of the ICD codes 86-93, 5589 as reported in PRISMANT and the reports of the Working Group on Clinical Virology, an estimation of hospitalisations caused by rotavirus compared to the total number of all gastro-enteritis hospital admissions can be made (Table 13, Table 14 and Figure 14).

**Table 13 PRISMANT data on gastro-enteritis hospitalisations among children < 5 years of age and estimations of rotavirus hospitalisations [110]**

| Year | Gastroenteritis Hospitalisations (n) | Estimated rotavirus (%) | Rotavirus Hospitalisations (n) |
|---|---|---|---|
| 2000 | 6016 | 47.6 | 2864 |
| 2001 | 6054 | 54.7 | 3312 |
| 2002 | 6172 | 51.2 | 3160 |
| 2003 | 7191 | 46.2 | 3322 |
| 2004 | 6423 | 46.7 | 3000 |
| 2005 | 7681 | 52.9 | 4063 |
| 2006 | 9393 | 52.2 | 4903 |
| 2007 | 8025 | 49.2 | 3948 |
| 2008 | 9492 | 62.1 | 5895 |
| 2009 | 8345 | 70.2 | 5917 |

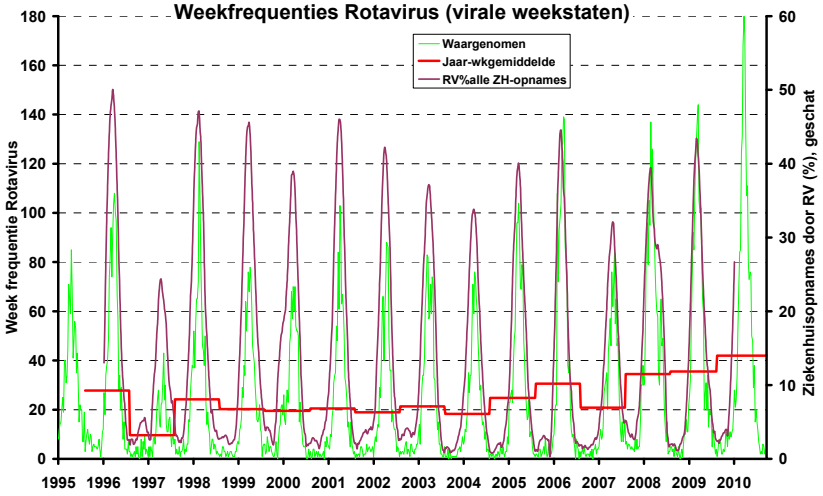



**Figure 14 Weekly reports of rotavirus positive results (Working Group on Clinical Virology) and the mean weekly frequency per year [110]. The estimated percentage of hospitalisations caused by rotavirus compared to all gastro-enteritis hospitalisations**

**Table 14 Weekly reports of rotavirus positive results of the Working Group on Clinical Virology and estimations of rotavirus hospitalisations, 1996-2009[110]**

| Year | Isolation frequency of Rotavirus (n) | Estimated % rotavirus compared to total number of GE hospitalisations |
|---|---|---|
| 1996 | 1395 | 22.2 |
| 1997 | 663 | 12.5 |
| 1998 | 1088 | 19.2 |
| 1999 | 1149 | 20.4 |
| 2000 | 946 | 16.5 |
| 2001 | 1066 | 18.4 |
| 2002 | 1011 | 16.6 |
| 2003 | 1079 | 15.4 |
| 2004 | 952 | 13.4 |
| 2005 | 1324 | 16.6 |
| 2006 | 1583 | 17.0 |
| 2007 | 1240 | 14.0 |
| 2008 | 1905 | 18.4 |
| 2009 | 1907 | 18.8 |

#### 4.1.3.1 Immune surveillance data

In the Dutch KOALA Birth Cohort Study, seroprevalence of rotavirus was measured at the age of 1 year in a birth cohort of infants born between March 1st 2002 and February 28th 2003 (n=612)[111]. Seroprevalence measured by IgG and IgA was 39% and 29%, respectively. Seropositivity for rotavirus was associated with a higher risk of recurrent wheeze in the first two years.

#### 4.1.3.2 Vaccine Effectiveness

Vaccine effectiveness studies have been performed in developed and developing countries. Both Rotarix and Rotateq appear to have less efficacy in developed countries compared to developing countries, although the effects are still reasonable.[112, 113]

In Finland, 20,736 infants were followed for hospitalisations and emergency department (ED) visits associated with rotavirus infection for up to three years after vaccination with pentavalent rotavirus vaccine (RV5).[114] A reduction in hospitalisations and ED visits of 94.0% was seen, which was highest for G1 (95.5%) and lowest for G2 (81.9%), compared to the placebo group. Evaluation of the efficacy of RV5 up to two years in a European cohort, including the above-mentioned Finnish children, showed a protection of 68.0% (95% CI, 60.3-74.4%) against rotavirus infection of any severity and it protected in particular against severe infection (98.3% (95% CI, 90.2-100%).[114] Furthermore, the vaccine was well tolerated.

A European study calculated cost-effectiveness for 5 countries and concluded that it was only cost-effective in Finland and not in Belgium, England and Wales, France and the Netherlands.[115, 116] Nevertheless, the cost-effectiveness of vaccination can easily change with changes in price of the vaccines and annual number of rotavirus cases. Although a vaccination programme in the Netherlands would be very effective in reducing numbers of RV infections of any severity in children younger than 5 years, the relatively low severity of non-fatal RV-GE cases and the very low number of avoided fatal cases per year does not result in a cost-effective programme.[117]

In Europe, Belgium, Austria, several states in Germany, Luxembourg and Finland have introduced universal vaccination. In Belgium, Rotarix and Rotateq were introduced in 2006 and 2007, respectively.[118] In the period from 2007-2009, the average vaccine coverage of all newborns was estimated at 85-90%. An overall decline was seen in the percentage of rotavirus positive cases compared to all hospitalised gastroenteritis cases of 34.7% in the first season up to 66.3% in the third season after vaccine introduction. In Austria, the coverage reached 87% in 2008.[119] After 1.5 years of vaccination, RV hospitalisations decreased in children aged younger than 2 years but not in the older children. Outside Europe, other countries have also started vaccination, including the United States and Australia. Nationally representative data on rotavirus vaccine coverage are not available for the United States.[120] However, it was estimated that the median coverage with 1 dose of rotavirus vaccine among infants aged 3 months has increased steadily since June 2006 and had reached 58% (range: 51%–68%) in December 2007. The 2007–2008 rotavirus season seemed to be delayed, shorter and diminished in magnitude compared with seasons before the implementation of rotavirus vaccination. The

extent of change appeared greater than expected on the basis of estimated vaccine coverage, suggesting indirect benefits to unvaccinated individuals from reduced viral transmission in the community. A retrospective analysis of health insurance claims data over two rotavirus seasons in the USA showed a vaccine effectiveness of 100% (95% CI: 87%–100%) for hospitalisations and ED visits for rotavirus gastroenteritis.{Wang, 2010 #89} In the outpatient setting, the effectiveness against rotavirus infection was 96% (95% CI: 76%–100%). A case-control study on the vaccine's effectiveness was conducted over a period of 5 months in Houston, Texas.{Boom, 2010 #90} Age-adjusted vaccine effectiveness against hospitalisation and ED visits for a full 3-dose series of RV5 was 88% (95% CI: 68%–96%). Vaccine effectiveness for two doses of RV5 was 81% (95% CI: 13%–96%) and that for one dose was 69% (95% CI: 13%–89%). Vaccine coverage in the first birth cohort in Australia was 73% for three doses, which led to a reduction of 89-94% of rotavirus hospitalisations.[121] A review by Tate et al. (2010) described declines in rotavirus disease in the USA and Australia, not only in vaccinated children, but also in children not eligible for vaccination, suggesting herd immunity.

### *4.1.4 Pathogen*

In 2009, 747 rotavirus positive samples were typed at the RIVM (personal communication Annelies Kroneman). G1[P8] was the most common type found (68.8%), followed by G4[P8] (13.7%) and G3[P8] (10.6%).

In 2008-2009, a study on gastroenteritis requiring hospitalisation was conducted in six Dutch hospitals (GEops study). Of the children (n= 96), 34% had a single infection of rotavirus and 22% had rotavirus together with one or more other pathogens. In the adults (n= 41), this was 12% and 10%, respectively. G1[P8] was most commonly found in children (35%), followed by G4[P8] (24%) and G3[P8] (15%). 44% Of the rotaviruses in the adults could not be typed, followed by G1[P8] (22%). In a European study among children younger than 5 years (n=3734) who were hospitalised or visited the ED because of community-acquired acute gastroenteritis, 43.4% was rotavirus-positive.[122] The four most common serotypes were G1[P8] (40.3%), G9[P8] (31.2%), G4[P8] (13.5%), and G3[P8] (7.1%). Although the overall decline of rotavirus positive cases in Belgium after implementation of a vaccination programme, the prevalence of the G2 genotype has sharply increased since 2006 and was responsible for 38.5% of infections in the 2008–2009 season (ref. Zeller). Furthermore, Matthijnssens et al. estimated that novel rotaviruses (e.g., a vaccine escape mutant) can spread worldwide in little more than a decade. Therefore, thorough and continuous surveillance is needed to detect such potential spreading at an early stage. (ref. Matthijnssens)

### *4.1.5 Adverse events*

Several trials were performed to evaluate the safety of rotavirus vaccine. Rotateq [123-125] as well as Rotarix [114, 126-128] showed a good safety profile and both vaccines were not associated with an increased risk of intussusception. Furthermore, no vaccine related serious adverse events were reported if the RIX4414 vaccine was reconstructed with other agents (e.g., water) instead of

CaCO3 buffer.[129] However, recently researchers made the unexpected finding that RotaTeq vaccines contained DNA from porcine circovirus 2 (PCV 2) and in Rotarix, DNA from porcine circovirus 1 (PCV 1) was found. PCV1 and PCV2 viruses are common in swine but, according to the FDA, not associated with illness in pigs or humans.[130, 131] The EMA found in a review that porcine trypsin, a reagent used in the vaccine production process, was the most likely cause for the presence of PCV and recommended that general guidance on this reagent should be developed. They also concluded that the presence of unexpected viral DNA in these vaccines does not pose a risk to public health.[132]

Finally, post-marketing reports have described severe gastroenteritis with vaccine viral shedding in infants who received rotavirus vaccine and were later diagnosed with severe combined immunodeficiency.[133-135] The US Food and Drug Administration recently approved labelling changes for Rotateq and Rotarix, contraindicating administration to individuals with a history of SCID.

#### *4.1.6 Current/ongoing research*

Laboratory for Infectious Diseases and Perinatal Screening of the RIVM participates in a European study on circulating serotypes of rotavirus. Furthermore, they monitor serotypes circulating in outbreaks in the Netherlands.

The Health Council is preparing a recommendation on rotavirus vaccination that will become available in 2011.

## 4.2 Varicella Zoster Virus (VZV) infection

*E.A. van Lier, H.J. Boot, J.M. Kemmeren, W. Luytjes and H.E. de Melker*

#### *4.2.1 Key points*

- While the incidence of hospitalised varicella cases in the Netherlands is lower than reported in other countries, the severity of varicella disease among hospitalised patients seems to be similar.
- No striking changes occurred in the VZV epidemiology in the Netherlands in 2009: the lower reported incidence of general practitioner consultations due to varicella in the Continuous Morbidity Registration (CMR) Sentinel General Practice Network in 2008/2009 is related to changes in the reporting system. Starting from 2008, the Netherlands Information Network of General Practice (LINH) will be used to calculate varicella incidence. This larger network of general practices includes CMR sentinel practices meeting quality criteria for electronic registration.
- The results for various studies (GP consultations, seroprevalence, cost-effectiveness, mathematical modelling) are expected in 2011 and will be input in the consideration of the Health Council on universal varicella vaccination.

### *4.2.2 Epidemiology*

#### 4.2.2.1 Incidence

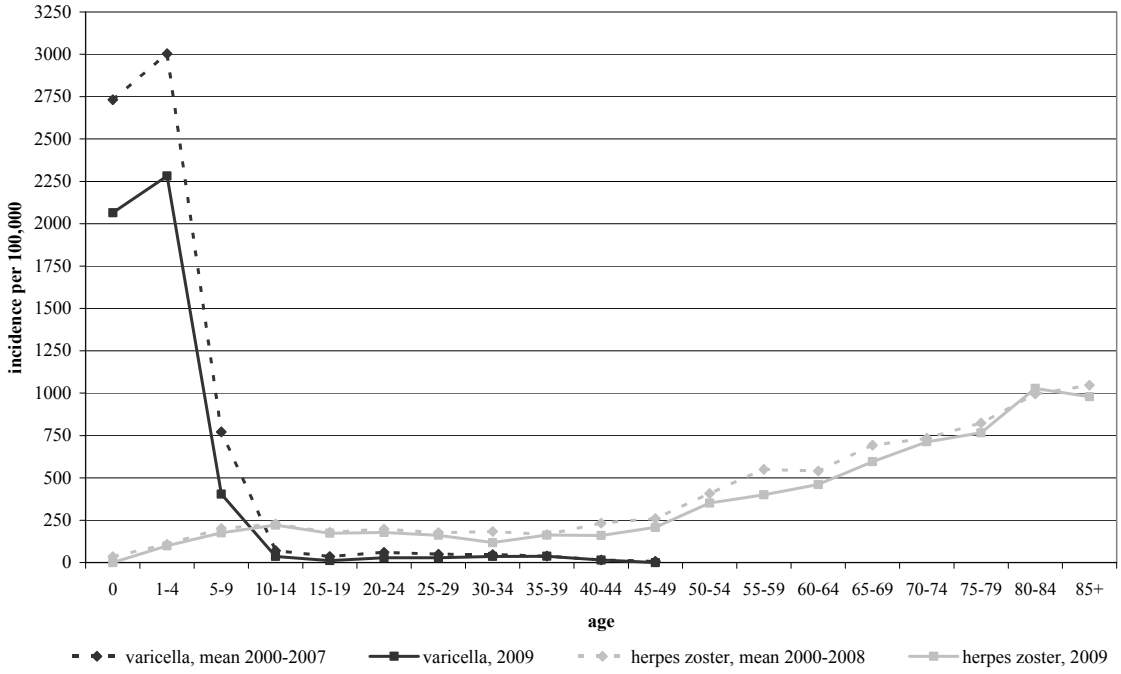
From the sentinel surveillance network of the Netherlands Institute of Primary Health Care (NIVEL), the number of patients with varicella or herpes zoster consulting a GP was obtained (Table 15).[136, 137 138] Starting in 2008, the sentinel Continuous Morbidity Registration (CMR) of NIVEL has changed from registration on paper to electronic reporting, which could have resulted in underreporting of the number of varicella patients.[136] Therefore, the NIVEL has advised to stop the CMR registration for varicella in 2011 and to use data from the Netherlands Information Network of General Practice (LINH) from 2008 onwards. For herpes zoster, the LINH registration has already been in use from 2002 onwards. From the literature it is known that periodic larger outbreaks of varicella occur with an inter-epidemic cycle of two to five years.[139] In contrast, the incidence of herpes zoster is stable over the years, which is consistent with the literature.[140] The incidence of GP consultations (per 100,000 inhabitants) because of varicella is highest in the age groups below 5 years, whereas for herpes zoster this is highest in the age groups above 50 years (Figure 15).[136-138]

**Table 15 Incidence, per 100,000, of GP consultations due to varicella or herpes zoster in 2000-2009 (rounded to tens)**

| Type | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|---|---|---|---|---|
| Varicella* | 200 | 240 | 320 | 270 | 250 | 190 | 300 | 210 | (160) | (110) |
| Varicella** | - | - | 190 | 160 | 200 | 130 | 260 | 230 | 310 | 180 |
| Herpes zoster* | 330 | 320 | - | - | - | - | - | - | - | - |
| Herpes Zoster** | - | - | 320 | 330 | 310 | 350 | 370 | 310 | 340 | 360 |

*Continuous Morbidity Registration (CMR) Sentinel General Practice Network [136, 138]

**Netherlands Information Network of General Practice (LINH)[137, 141]




Note: varicella cases in persons older than 49 are only sporadically reported by GPs and are therefore not included.

**Figure 15 Incidence of GP-consultations per 100,000 for varicella and herpes zoster incidence in 2009 versus mean incidence in 2000-2008** [136,137,138]

#### 4.2.2.2 Hospitalisation

The numbers of hospitalisations with discharge code varicella (ICD-9 group 052) or herpes zoster (ICD-9 group 053) were obtained from the registry of Prismant (National Medical Register)[142] and the incidence is displayed in Table 16. Since 2006, the coverage of the National Medical Register varies. Only clinical admissions were included (admissions for one day were excluded). The incidence of herpes zoster hospital admissions is – like the GP consultations – stable in the period 2000-2009. The incidence of hospital admissions due to main diagnosis varicella is highest among 0-year olds and for herpes zoster highest among the oldest age groups (Figure 16)

**Table 16 Incidence per 100,000 of hospitalisations due to main and side diagnosis varicella or herpes zoster, 2000-2009** [142]

| Type | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|---|---|---|---|---|
| Varicella | | | | | | | | | | |
| - main | 1.3 | 1.5 | 1.4 | 1.7 | 1.7 | 1.5 | 2.0 | 1.4 | 1.7 | 1.5 |
| - main + side | 2.0 | 2.3 | 2.2 | 2.5 | 2.6 | 2.2 | 2.9 | 2.2 | 2.4 | 2.2 |
| Herpes zoster | | | | | | | | | | |
| - main | 2.3 | 2.5 | 2.7 | 2.2 | 2.5 | 2.2 | 2.0 | 2.0 | 2.1 | 2.4 |
| - main + side | 5.0 | 4.9 | 5.1 | 4.9 | 5.0 | 4.3 | 4.0 | 4.0 | 4.0 | 4.6 |

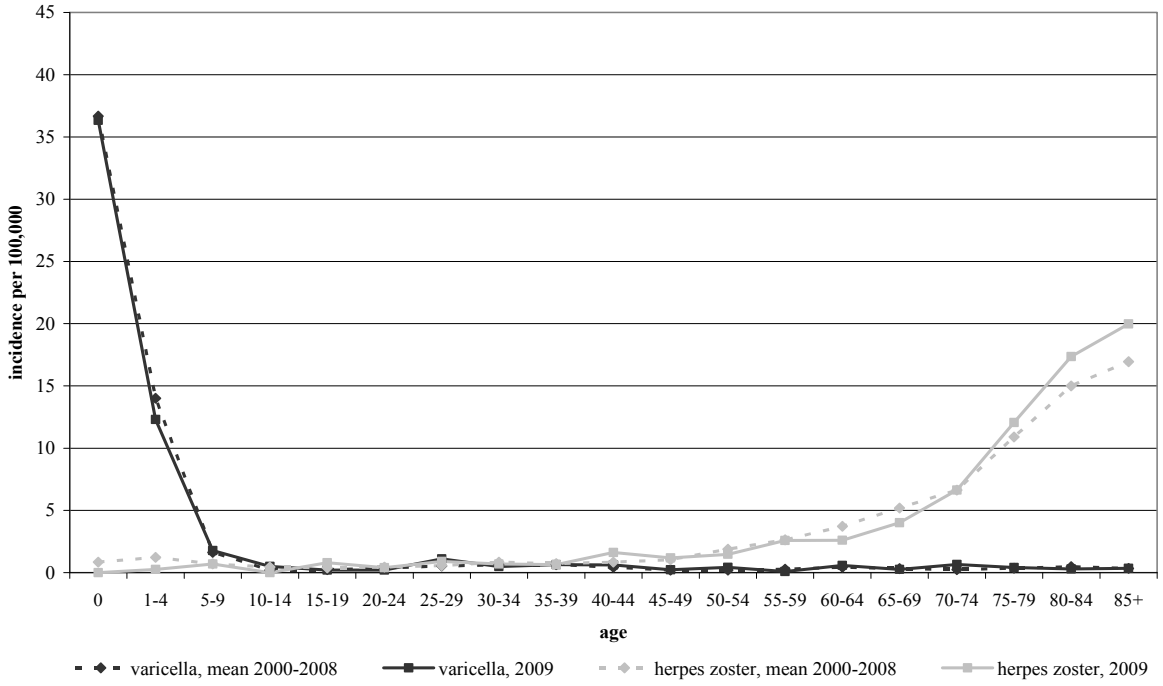



**Figure 16 Incidence of hospitalisations per 100,000 for main diagnosis varicella and herpes zoster, incidence 2009 versus mean incidence 2000-2008** [142]

#### 4.2.2.3 Deaths

The number of deaths due to main diagnosis varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02) were derived from CBS (Table 17).[80] In 2009 there was one reported death with main cause of death varicella and 20 deaths with main cause of death herpes zoster.

**Table 17 Number of deaths with main cause of death varicella or herpes zoster, 2000-2009.** [80]

| Type | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|---|---|---|---|---|
| Varicella | 1 | 3 | 4 | 6 | 4 | 1 | 3 | 5 | 0 | 1 |
| Herpes zoster | 14 | 13 | 26 | 14 | 15 | 15 | 24 | 21 | 14 | 20 |

### *4.2.3 Pathogen*

VZV isolates can be divided in five distinct clades on the basis of phylogenetic analyses of whole-genome sequences. World-wide distribution of isolates among these clades is mainly based upon the geographic origin of the isolate. In Europe, clade 1 strains are most prevalent.[143] Although recombination of strains belonging to different clades has been reported (including the OKA-vaccin strain)[144], no impact of recombination on vaccine effectiveness is currently evident. Introduction of universal varicella vaccination should be accompanied by molecular surveillance to monitor the impact of the vaccination on the distribution of wild-type VZV and the emerge of wild-type/vaccine recombinants.

### *4.2.4 Adverse events*

#### 4.2.4.1 Varicella vaccination

In February 2008, preliminary evidence of a twofold increased risk of febrile seizure after the combination MMRV vaccine when compared with separate MMR and varicella vaccines were published. This year, similar results were found with data on twice as many vaccine recipients.[145] Based on these results and after consideration of post-licensure data and other evidence, ACIP adopted new recommendations regarding the use of MMRV vaccine for the first and second doses and identified a personal or family history of seizure as a precaution for the use of MMRV vaccine.[146] For the first dose of measles, mumps, rubella and varicella vaccines at age 12-47 months, either MMR vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMRV vaccine, CDC recommends that MMR vaccine and varicella vaccine should be administered for the first dose in this age group. For the second dose of measles, mumps, rubella and varicella vaccines at any age (15 months-12 years) and for the first dose at age >+ 48 months, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and varicella vaccine).

A study examining the safety and reactogenicity of a booster dose of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) co-administered with MMRV vaccine, showed that both vaccines can be co-administered without compromising safety.[62]

In general, the Oka/Merck varicella vaccine (VARIVAX®) is well tolerated and most adverse events are non-serious. The rate of adverse events in Europe (3 reports per 10,000 doses in the first 5 years after introduction in Europe) was very similar to the global rate (3.4 reports per 10,000 doses in the first 10 years of experience with the vaccine).[147]

#### 4.2.4.2 Herpes zoster vaccination

Although several studies showed that herpes zoster vaccine is effective in preventing herpes zoster, its safety has not been described in depth. Therefore, Simberkoff assessed local adverse effects and short- and long-term safety profiles of herpes zoster vaccine in immuno-competent older adults. They found low rates of acute local reactions and, across the study population, no detectable effects on the rates of serious adverse events during the 42 days after inoculation or on the rates of death during the entire mean 3.39 years of follow-up.[148] Mills et al. conducted a study to evaluate the safety of zoster vaccine recipients who had had a prior episode of herpes zoster. They found no serious AEs within the 28-day safety follow-up period. Although a higher percentage of subjects reported injection-site AEs after receiving zoster vaccine (45.9%) than did placebo recipients (4.2%), the proportion of subjects reporting systemic clinical AEs was similar in both groups (15.3% vs. 13.5%).[149] A study with the aim to establish whether adverse events are associated with wild-type or vaccine varicella zoster virus strain, also showed that

the VZV is generally well tolerated.[147] Finally, adverse events were also minor and similar in HIV-infected vaccine and placebo recipients.[150]

### 4.2.5 *Current/ongoing research*

Medical record research among patients hospitalised with varicella in 2003-2006 indicated that the severity of varicella among hospitalised patients in the Netherlands does not differ from other countries, despite a lower number of hospitalised cases in the Netherlands compared with other countries (van Lier A, van der Maas NAT, Rodenburg GD, Sanders EAM and de Melker HE. Hospitalisation due to varicella in the Netherlands; article submitted).

In 2009, the potential effects of programmatic herpes zoster vaccination on the elderly in the Netherlands were assessed.[151] In 2010, research was started on the cost-effectiveness of varicella vaccination. An important source of information is the Integrated Primary Care Information (IPCI) database. This database will not only provide information on the incidence of GP consultations due to varicella, but also on the number and type of visits per patient, prescriptions, complications and referrals to a specialist or hospital. At the end of 2010, new data on the seroprevalence of VZV will become available (Pienter 2 project), which will provide information on the occurrence of varicella in the Dutch population. These data could be used in a future dynamic transmission model in which the possible effects of varicella vaccination on the occurrence of herpes zoster will be incorporated as well.

It will be necessary to discuss the above information in the Dutch Health Council and the desirability of whether or not to introduce universal vaccination against varicella. The United States was the first country that introduced universal childhood varicella vaccination. Their vaccination programme started in 1995 and has reduced overall disease incidence by 57% to 90%, hospitalisations by 75% to 88%, deaths by >74% and direct inpatient and outpatient medical expenditures by 74%.[152] In Germany, where varicella vaccination was recommended in 2004 and included in the NIP in 2006, sentinel data from April 2005 to March 2009 showed a reduction of 55% in varicella cases in all ages.[153]

One of the concerns is the feasibility of reaching a high vaccination coverage in the Netherlands. In the United States the vaccine coverage among children aged 19 to 35 months increased nationally from 27% in 1997 to 89% in 2006.[152] Different studies in Germany showed that the overall coverage increased to more than fifty per cent, indicating increasing acceptance by parents and physicians, but the WHO-defined goal of 85% has not yet been reached.[154, 155]

Another concern regarding introduction of universal varicella vaccination is the possible increase of herpes zoster in the mid-term (the first 30-50 years after start of vaccination).[156] So far, there is insufficient data in the United States to draw conclusions on the impact of routine childhood varicella vaccination on the incidence of herpes zoster.[157] In Australia (where

universal varicella vaccination was introduced in 2005) there are indications that the incidence of herpes zoster is increasing but it is not clear if this rise can be attributed to the varicella immunisation programme.[158, 159]

## 4.3 Hepatitis A

*L.P.B. Verhoef, I.H.M. Friesema, J.M. Kemmeren*

### *4.3.1 Key points*

- The susceptible population in the Netherlands is increasing in age, which is a point of concern that should be the future focus for public health action.
- Elderly people borne after World War II would benefit from HAV vaccination because they are likely to be susceptible, develop clinically serious symptoms after infection and are increasingly at risk of exposure through imported viruses through foods or travellers.
- The long-term decreasing trend since the early nineties continues (269 cases in 2008, 178 cases in 2009)
- Almost half of all cases is travel related (42%)
- Aluminium-free HAV vaccines are considered more suitable for intradermal use than traditional vaccines
- Inactivated hepatitis A vaccine is very effective

### *4.3.2 Changes in vaccine 2009-2010-2011*

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### *4.3.3 Epidemiology*

The number of notified cases of hepatitis A in the Netherlands decreased from 269 cases in 2006 to 178 cases in 2009 (1.65 per 100,000 population to 1.08 per 100,000 population).[160] This corresponds with the long-term decreasing trend since the early nineties.

In 2009, most cases (74 cases, 42%) were reported to be travel-related, mostly after a visit to Morocco (25 cases, 14%). This is in line with data from previous years (43% in 2008, 51% in 2007, 44% in 2006, 54% in 2005 and 39% in 2004) and the reason why Municipal Health Services in the Netherlands have carried out HAV vaccination programmes since 1998, focused on immigrants' children, to reduce import and secondary HAV infections.[161]

In 2009, a total of 33 cases (19%) were secondary cases infected by closely related persons, of which 8 (4%) following MSM contacts. Nine cases (5%) appeared to be related to food or water. The source of infection was unknown for the remaining cases, also due to the long incubation period.

*Immunosurveillance:*

The prevalence of antibodies to hepatitis A (HAV) was assessed in the nationwide sample (n=6,229) in the Netherlands in 2006-7 (Pienter 2), and compared to the seroprevalence in a

similar study in 1995-6 (n=7,376) (Pienter 1). The overall weighted seroprevalence in 2006-2007 was 39.3% (95%CI 37.0%-41.6%), which was significantly higher than the 33.9% (95%CI 31.8-36.0) in 1995-1996. The seroprevalence did not significantly differ between sexes (37.3%, 95%CI 34.4%-40.3% for men and 41.3%, 95%CI 38.6%-43.9% for women). Of the study population in the 2006-2007 study, 87.4% was not vaccinated and the seroprevalence for this group was 30.6% (95% CI 28.4%-32.8%). In the first study, 99.2% of the study population was not vaccinated and the seroprevalence for this group was 30.3% (24.4%-36.1%), which did not significantly differ from that found in the second study. The age-dependent seroprevalence for non-HAV-vaccinated persons in the first and second study are plotted per year of age in Figure 1, showing a cohort effect, i.e., persons born after World War II were susceptible in 1995-1996 and are still susceptible in 2006-2007. A relatively high seroprevalence was seen among infants of <1 year of age (18%, 95%CI 12-23%), which is a reflection of maternally derived antibodies.[162]

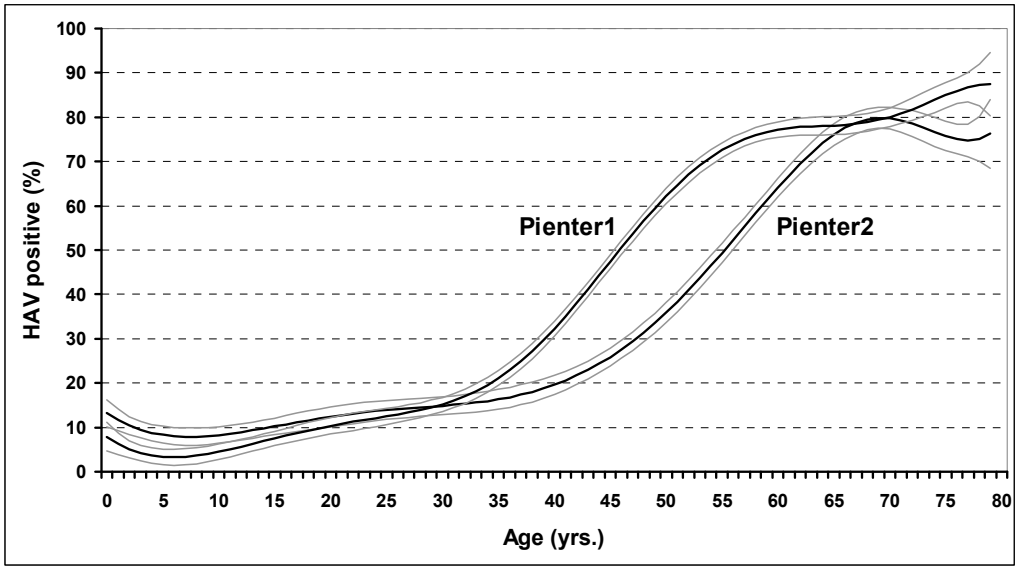


**Figure 17: Age-prevalence of hepatitis A antibodies presented per age-year including 90% confidence intervals in non-HAV-vaccinated persons in 2 nationwide samples of the Dutch population in 1995-1996 (first study, dashed line, n=7,287, excluding 59 vaccinated participants) and 2006-2007 (n=5442, continuous line, excluding 786 vaccinated participants).**

### *4.3.4 Pathogen*

In 2010, molecular surveillance of hepatitis A cases revealed a cluster of geographically scattered cases with an identical and unique strain, reported with an unknown source within the Netherlands. Two of 11 primary patients needed liver transplantation after acute liver failure.[163] An outbreak study was performed and identified semi-dried tomatoes as the potential source of infection.[164] It seemed to be an international problem, since outbreaks pointing to semi-dried tomatoes were seen in Australia with an identical strain and in France, with a closely related strain.

### 4.3.5 *Adverse events*

Aluminium-free HAV vaccines are considered more suitable for intradermal use than traditional vaccines, which can cause long-lasting local reactions. Frösner et al. compared the safety of an aluminium-free virosomal HAV vaccine administered by different routes: intradermal, subcutaneous, and intramuscular. The results show that all routes of administration were well tolerated. However, local reactions were more common in subjects vaccinated intradermally and subcutaneously than intramuscularly.[165]

Beran et al. compared the long-term persistence of anti-HAV and anti-HBs antibodies up to ten years after the subjects had received either a two-dose schedule of an Adult formulation of combined hepatitis A and B vaccine or a three-dose schedule of the Paediatric formulation of the vaccine. None of the SAEs reported during the long-term follow-up period were assessed by the investigator to be vaccine-related or due to any study procedure.[166]

Radzikowski et al. evaluated the safety of an inactivated hepatitis A vaccine in paediatric patients with Inflammatory Bowel Disease. There were no serious adverse events related to HAV during the study. Furthermore, no differences in local and systemic side effects were found between the patient and control group.[167]

### 4.3.6 *Current/ongoing research*

In general, people at risk of HAV infection are those born after World War II, which is attributed to the turning point of the hygiene standard at that time in the Netherlands.[168] Recent findings indicated that the population at risk in the Netherlands is an ageing cohort and expected to be a future public health concern.[162] Previous reports have already concluded that mass vaccination programmes would probably not be cost-effective. However, vaccination targeted at population groups at risk of infection was previously found to be cost effective[169], and vaccination programmes can result in incidence reduction through herd immunity.[170]

Although the elderly may not be a group with increased risk of infection, this group is at risk of severe illness once infected.[171] For this reason, although universal vaccination may not be cost-effective, it is more likely to reduce incidence and mortality compared to vaccination targeted at groups at risk of infection.[172] This could be a lead for further research, education and/or specific vaccination programmes.

The currently applied inactivated hepatitis A vaccine can be considered very effective. Waning immunity, i.e., decline of antibodies over the years, have not resulted in an HAV antibodies amount below the protection level within 12 years[173] and immunity is expected to be lifelong. The use of the vaccine as post-exposure prophylaxis can also be considered effective.

Victor et al. have compared the effectiveness of hepatitis A vaccine (VAQTA) and immunoglobulin after exposure to the hepatitis A virus in a randomised trial in Kazakhstan.[174] A

total of 1,090 contacts of index cases of hepatitis A, which were susceptible to the virus, were randomly assigned 1 dose of either the vaccine or the immunoglobulin. Rates of symptomatic infection with hepatitis A were low in both groups, although slightly higher in the vaccine group (4.4% compared to 3.3%). They concluded that hepatitis A vaccine may be a reasonable alternative to immunoglobulin for post-exposure prophylaxis.

## 4.4 Meningococcal serogroup B disease

*S.C. de Greeff, W.A.M. Berbers, L.M. Schouls and J.M. Kemmeren*

### *4.4.1 Key points*

- Currently, there is no vaccine against infections with serogroup B meningococci.

### *4.4.2 Changes in vaccine 2009-2010-2011*

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### *4.4.3 Epidemiology*

Since 2000 the number of patients with meningococcal B disease has been decreasing, as can be seen in Figure 17 and Table 18. In 2009 the number of cases had decreased to 117. The reason for this decreased incidence remains enigmatic. Possibly, natural fluctuation may explain this decreasing trend.

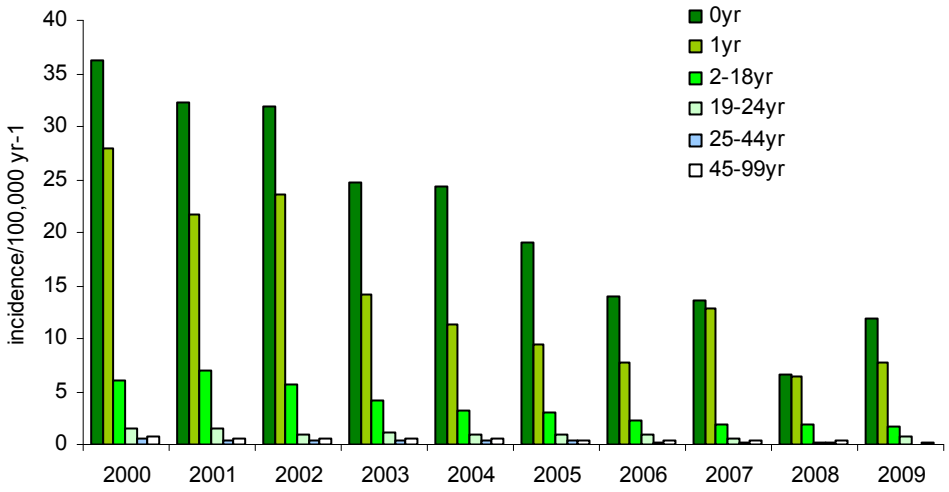


**Figure 17 Age-specific incidence of MenB disease by year, 2001-2009**

**Table 18 Absolute number of patients with MenB disease per age-category from 2000-2009**

| Age (Yrs) | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 73 | 67 | 65 | 50 | 49 | 37 | 26 | 25 | 12 | 22 |
| 1 | 56 | 44 | 49 | 29 | 23 | 19 | 15 | 24 | 12 | 14 |
| 2-18 | 198 | 233 | 189 | 142 | 110 | 102 | 75 | 64 | 65 | 56 |
| 19-24 | 17 | 18 | 11 | 13 | 10 | 11 | 12 | 7 | 3 | 8 |
| 25-44 | 30 | 22 | 20 | 23 | 14 | 16 | 10 | 7 | 5 | 3 |
| 44-99 | 43 | 36 | 39 | 36 | 32 | 27 | 20 | 21 | 26 | 14 |
| **Total** | **417** | **420** | **373** | **293** | **238** | **212** | **158** | **148** | **123** | **117** |

*Immune surveillance*
No new observations.

### *4.4.4 Pathogen*

No change in the composition of the MenB population circulating in the Netherlands has been observed.

### *4.4.5 Adverse events*

Two phase I trials evaluated the safety and reactogenicity of experimental MenB vaccines. Both vaccines were well tolerated and no serious adverse events related to vaccination were reported. Pain at the injection site, upper respiratory symptoms, fatigue and headache were the most commonly reported adverse events.[175, 176]

### *4.4.6 Current/ongoing research*

Novartis wants to apply for a license for their MenB vaccine (4CMenB) in the near future. The filing will be mainly based on the comprehensive data set of more than 7,500 children obtained in 2 large phase III trials (one trial is finished and the second one will be completed this year). There are no efficacy data and the filing in the EU will be based on the immunogenicity (SBA titers), tolerability and safety profile of the vaccine obtained by a comprehensive clinical programme. The vaccine consists of three protein components (factor H-binding protein (fHBP), Neisserial Heparin binding antigen (NHBA) and Neisserial adhesin A (NadA)) and is completed by the addition of the OMV vaccine for New Zealand (PorA P1.7-2,4, MeNZB).

The development of the MenB vaccine from Pfizer (formerly Wyeth) has obviously not progressed this far. Their vaccine consists of two variants of fHBP.

There is still some scepticism about the coverage of these MenB vaccines due to the hypervariability of the biological relevant proteins, despite a number of presentations at the 17$^{th}$ IPNC (international pathogenic *Neisseria* conference), which claimed that coverage could be as high as 100%. NVI is working on a second-generation NonaMen (9-valent PorA OMV vaccine) based on class 4 negative and mutated LPS (LpxL1) strains.

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# Appendix 1 Mortality and morbidity figures per disease from the various data sources

Mortality data were retrieved from
http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=7233&D1=0&D2=0&D3=0&D4=a&HDR=G2,G1,G3&STB=T&VW=T

Data on notifications were retrieved from
http://www.rivm.nl/cib/infectieziekkten-A-Z/Epidemiologie/aiz/

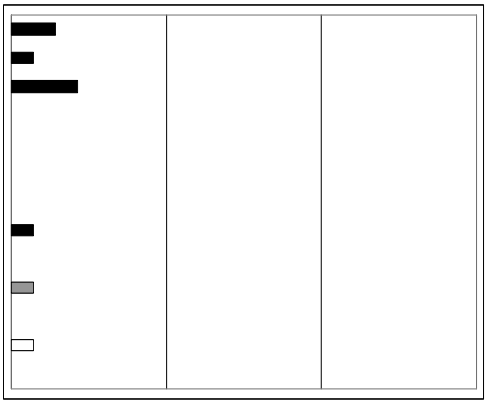
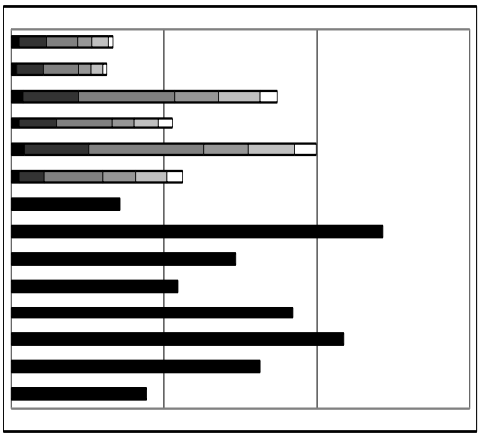
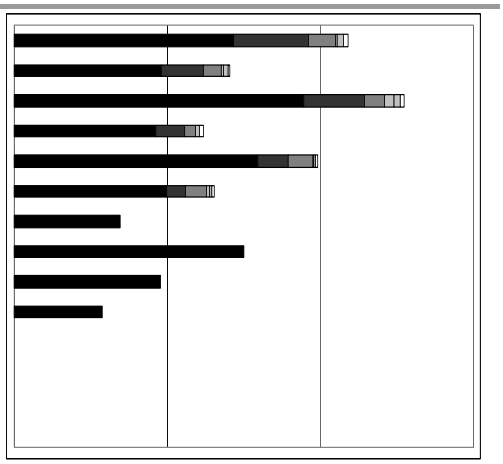
Data on hospitalisations were retrieved from the National Medical Register, Prismant Utrecht.

Data on isolates of *Haemophilus influenzae* serotype b, meningococcal and pneumococcal disease were retrieved from the Netherlands Reference laboratory for Bacterial Meningitis (NRBM). The isolates of the other diseases discussed in this report are own data, sent to RIVM for typing.

**Diphtheria** **ICD9 032.0-3, 032.8-9** **ICD10 A36**

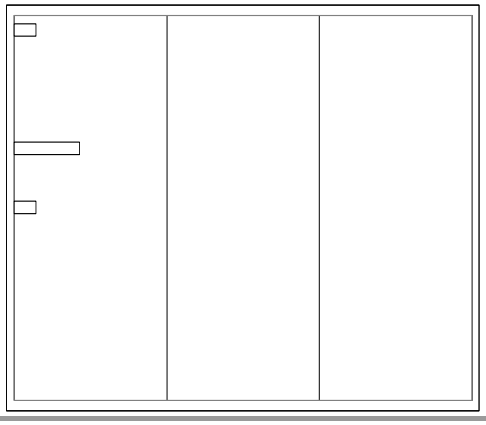
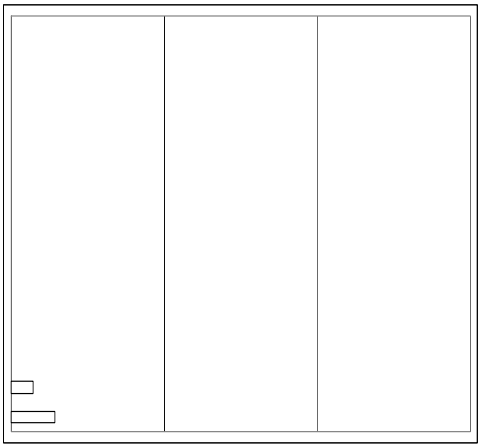
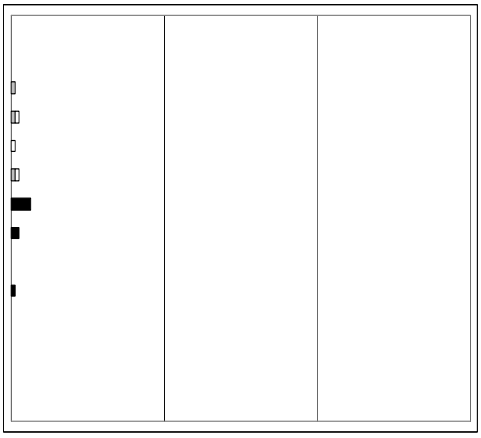
| | | Age (Years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **0** | **1-4** | **5-9** | **10-19** | **20-49** | **50+** | **Total** | N |
| Mortality | 1997 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 1998 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 1999 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Notifications | 1997 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | |
| | 1998 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 1999 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2010 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Hospitalisation | 1997 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 1998 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| | 1999 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2000 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | |
| | 2001 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | |
| | 2002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Isolates | 2001 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| | 2004 | - | - | - | - | - | - | 1 | |
| | 2007 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | |

**Pertussis** **ICD9 033.0-1, 033.8-9** **ICD10 A37**

| | | Age (Years) 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | Total | N |
|---|---|---|---|---|---|---|---|---|---|
| Mortality | 1997 | 2 | 0 | 0 | 0 | 0 | 0 | 2 |  |
| | 1998 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | |
| | 1999 | 3 | 0 | 0 | 0 | 0 | 0 | 3 | |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2004 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | |
| | 2005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2006 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | |
| | 2007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| | 2009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Notifications | 1997 | 213 | 705 | 821 | 379 | 420 | 126 | 2671 |  |
| | 1998 | 134 | 714 | 921 | 316 | 310 | 108 | 2508 | |
| | 1999 | 307 | 1447 | 2526 | 1153 | 1084 | 447 | 6980 | |
| | 2000 | 211 | 976 | 1460 | 564 | 648 | 363 | 4229 | |
| | 2001 | 343 | 1676 | 3011 | 1169 | 1207 | 587 | 8030 | |
| | 2002 | 198 | 666 | 1540 | 856 | 810 | 417 | 4487 | |
| | 2003 | - | - | - | - | - | - | 2847 | |
| | 2004 | - | - | - | - | - | - | 9723 | |
| | 2005 | - | - | - | - | - | - | 5867 | |
| | 2006 | - | - | - | - | - | - | 4370 | |
| | 2007 | - | - | - | - | - | - | 7374 | |
| | 2008 | - | - | - | - | - | - | 8704 | |
| | 2009 | - | - | - | - | - | - | 6503 | |
| | 2010 | - | - | - | - | - | - | 3551 | |
| Hospitalisation | 1997 | 287 | 97 | 36 | 2 | 8 | 6 | 436 |  |
| | 1998 | 192 | 55 | 23 | 4 | 6 | 2 | 282 | |
| | 1999 | 378 | 80 | 26 | 12 | 8 | 5 | 509 | |
| | 2000 | 185 | 38 | 14 | 5 | 0 | 5 | 247 | |
| | 2001 | 318 | 40 | 33 | 1 | 2 | 3 | 397 | |
| | 2002 | 199 | 25 | 27 | 4 | 3 | 3 | 261 | |
| | 2003 | - | - | - | - | - | - | 138 | |
| | 2004 | - | - | - | - | - | - | 300 | |
| | 2005 | - | - | - | - | - | - | 191 | |
| | 2006 | - | - | - | - | - | - | 115 | |
| | 2007 | | | | | | | | |
| | 2008 | | | | | | | | |
| | 2009 | | | | | | | | |
| | 2010 | | | | | | | | |

**Tetanus** **ICD9 037, 7713**

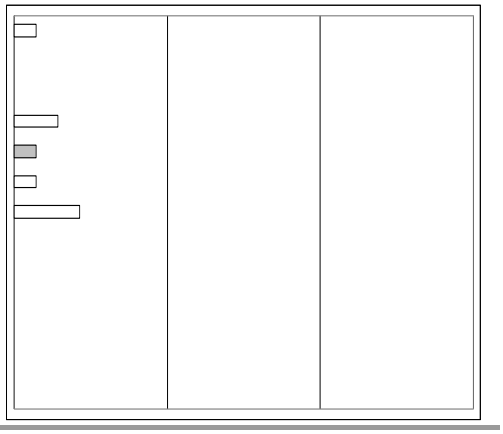
**ID10 A33-35**

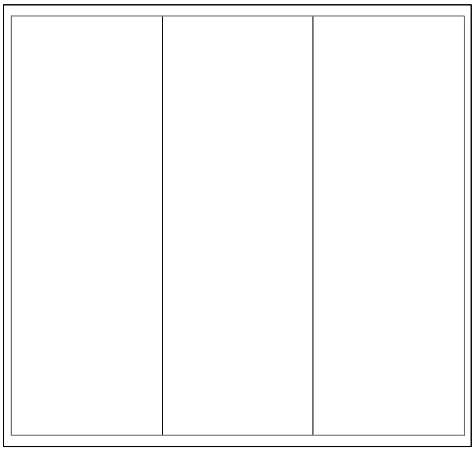
| | | Age (Years) | | | | | | | N |
|---|---|---|---|---|---|---|---|---|---|
| | | **0** | **1-4** | **5-9** | **10-19** | **20-49** | **50+** | **Total** | |
| Mortality | 1997 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |  |
| | 1998 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 1999 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | |
| | 2002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2003 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| | 2004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Notifications | 1997 | 0 | 0 | 0 | 0 | 1 | 4 | 5 |  |
| | 1998 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 1999 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2009 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| | 2010 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | |
| Hospitalisation | 1997 | - | - | - | - | - | - | - |  |
| | 1998 | - | - | - | - | - | - | - | |
| | 1999 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | |
| | 2000 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| | 2002 | 0 | 0 | 0 | 1 | 0 | 1 | 2 | |
| | 2003 | - | - | - | - | - | - | 5 | |
| | 2004 | - | - | - | - | - | - | 2 | |
| | 2005 | - | - | - | - | - | - | 0 | |
| | 2006 | - | - | - | - | - | - | 1 | |
| | 2007 | - | - | - | - | - | - | - | |
| | 2008 | - | - | - | - | - | - | - | |
| | 2009 | - | - | - | - | - | - | - | |
| | 2010 | - | - | - | - | - | - | - | |

**Poliomyelitis** **ICD9 045.0-2, 045.9**

**ICD10 A80**

| | | Age (Years) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **0** | **1-4** | **5-9** | **10-19** | **20-49** | **50+** | **Total** |
| Mortality | 1997 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| | 1998 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1999 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 2 | 2 |
| | 2001 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| | 2002 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| | 2003 | 0 | 0 | 0 | 0 | 0 | 3 | 3 |
| | 2004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Notifications | 1997 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1998 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1999 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2010 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |





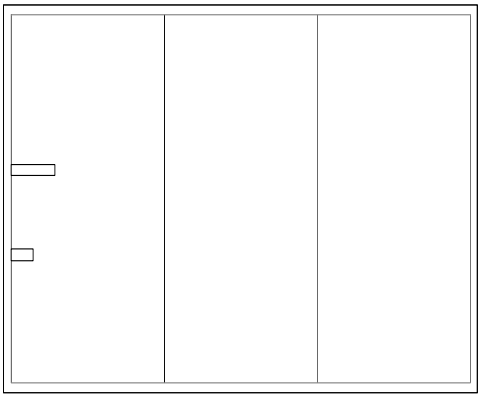
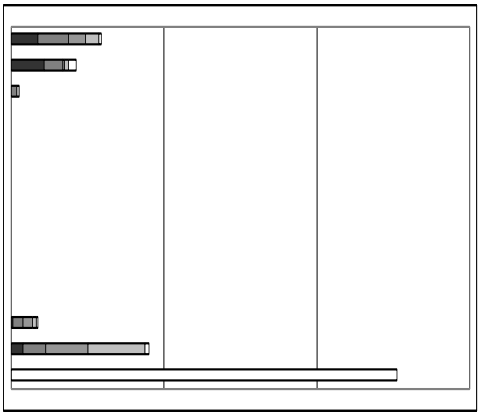
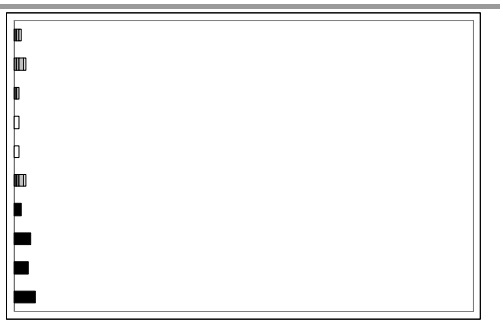
**Hib** **ICD9 3200**

**ICD10 A41.5 G00.0**

| | | Age (Years) | | | | | | | N |
|---|---|---|---|---|---|---|---|---|---|
| | | **0** | **1-4** | **5-9** | **10-19** | **20-49** | **50+** | **Total** | |
| Notifications | 1997 | - | - | - | - | - | - | - | |
| | 1998 | - | - | - | - | - | - | - | |
| | 1999 | - | - | - | - | - | - | - | |
| | 2000 | - | - | - | - | - | - | - | |
| | 2001 | - | - | - | - | - | - | - | |
| | 2002 | - | - | - | - | - | - | - | |
| | 2003 | - | - | - | - | - | - | - | |
| | 2004 | - | - | - | - | - | - | - | |
| | 2005 | - | - | - | - | - | - | - | |
| | 2006 | - | - | - | - | - | - | - | |
| | 2007 | - | - | - | - | - | - | - | |
| | 2008 | - | - | - | - | - | - | - | |
| | 2009 | 1 | 6 | 0 | 0 | 1 | 7 | 15 | |
| | 2010 | - | - | - | - | - | - | 33 | |
| Isolates | 1997 | 5 | 5 | 0 | 0 | 1 | 8 | 19 | |
| | 1998 | 5 | 6 | 3 | 0 | 1 | 4 | 19 | |
| | 1999 | 4 | 3 | 1 | 0 | 1 | 3 | 12 | |
| | 2000 | 3 | 5 | 0 | 0 | 3 | 4 | 15 | |
| | 2001 | 3 | 5 | 0 | 1 | 4 | 4 | 17 | |
| | 2002 | 7 | 9 | 0 | 0 | 6 | 9 | 31 | |
| | 2003 | - | - | - | - | - | - | 49 | |
| | 2004 | - | - | - | - | - | - | 43 | |
| | 2005 | - | - | - | - | - | - | 24 | |
| | 2006 | - | - | - | - | - | - | | |
| | 2007 | - | - | - | - | - | - | | |
| | 2008 | - | - | - | - | - | - | | |
| | 2009 | - | - | - | - | - | - | | |
| | 2010 | | | | | | | | |

**Mumps** **ICD9 072.0-3, 072.7-9**

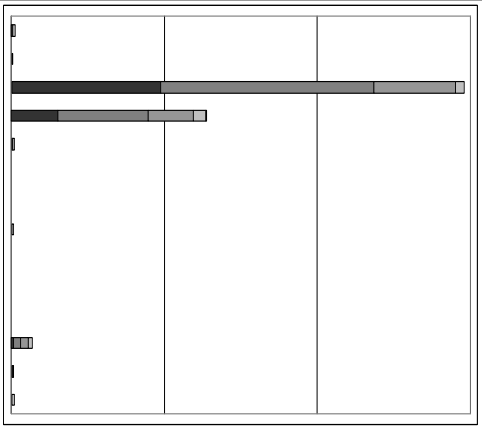
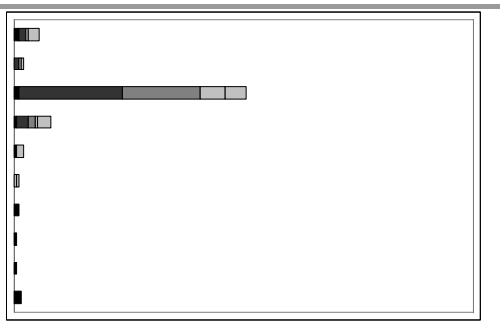
**ICD10 B26**

| | | Age (Years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **0** | **1-4** | **5-9** | **10-19** | **20-49** | **50+** | **Total** | N |
| Mortality | 1997 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
| | 1998 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 1999 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2002 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | |
| | 2003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2005 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| | 2006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Notifications | 1997 | 0 | 14 | 16 | 9 | 7 | 1 | 47 |  |
| | 1998 | 0 | 17 | 10 | 1 | 2 | 4 | 34 | |
| | 1999* | 0 | 0 | 3 | 0 | 1 | 0 | 4 | |
| | 2000 | - | - | - | - | - | - | - | |
| | 2001 | - | - | - | - | - | - | - | |
| | 2002 | - | - | - | - | - | - | - | |
| | 2003 | - | - | - | - | - | - | - | |
| | 2004 | - | - | - | - | - | - | - | |
| | 2005 | - | - | - | - | - | - | - | |
| | 2006 | - | - | - | - | - | - | - | |
| | 2007 | - | - | - | - | - | - | - | |
| | 2008* | 0 | 1 | 5 | 5 | 2 | 1 | 14 | |
| | 2009 | 0 | 6 | 12 | 22 | 30 | 2 | 72 | |
| | 2010 | - | - | - | - | - | - | 202 | |
| Hospitalisation | 1997 | 0 | 1 | 0 | 0 | 1 | 1 | 3 |  |
| | 1998 | 0 | 0 | 1 | 1 | 2 | 1 | 5 | |
| | 1999 | 0 | 1 | 0 | 0 | 1 | 0 | 2 | |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | |
| | 2002 | 0 | 1 | 1 | 2 | 0 | 1 | 5 | |
| | 2003 | - | - | - | - | - | - | 3 | |
| | 2004 | - | - | - | - | - | - | 7 | |
| | 2005 | - | - | - | - | - | - | 6 | |
| | 2006 | - | - | - | - | - | - | 9 | |
| Isolates | 1997 | - | - | - | - | - | - | 19 |  |
| | 1998 | - | - | - | - | - | - | 9 | |
| | 1999 | - | - | - | - | - | - | 6 | |
| | 2000 | - | - | - | - | - | - | 8 | |
| | 2001 | - | - | - | - | - | - | 2 | |
| | 2002 | - | - | - | - | - | - | 8 | |
| | 2003 | - | - | - | - | - | - | 6 | |
| | 2004 | - | - | - | - | - | - | 7 | |
| | 2005 | - | - | - | - | - | - | 12 | |
| | 2006 | - | - | - | - | - | - | 9 | |
| | 2007 | - | - | - | - | - | - | 9 | |
| | 2008 | - | - | - | - | - | - | 80 | |

* No notifications between April 1st 1999 – December 31st 2008

**Measles** **ICD9 055.0-2, 055.7-9**

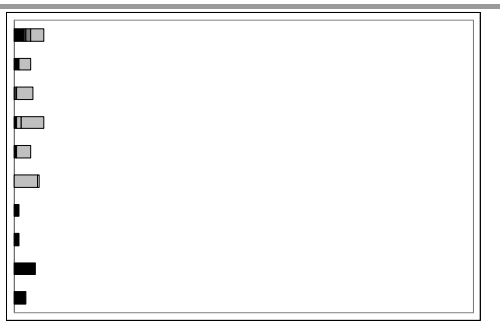
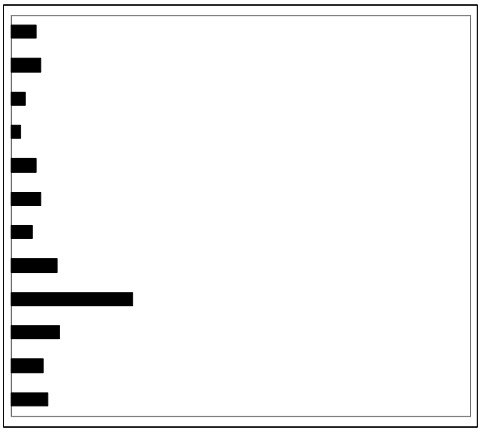
**ICD10 B05**

| | | Age (Years) | | | | | | | N |
|---|---|---|---|---|---|---|---|---|---|
| | | **0** | **1-4** | **5-9** | **10-19** | **20-49** | **50+** | **Total** | |
| Mortality | 1997 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
| | 1998 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | |
| | 1999 | 0 | 1 | 0 | 1 | 0 | 0 | 2 | |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2003 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | |
| | 2004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Notifications | 1997 | 1 | 9 | 0 | 0 | 11 | 0 | 21 |  |
| | 1998 | 1 | 1 | 2 | 2 | 3 | 0 | 9 | |
| | 1999 | 41 | 738 | 1112 | 427 | 44 | 6 | 2368 | |
| | 2000 | 19 | 225 | 469 | 237 | 64 | 5 | 1019 | |
| | 2001 | 0 | 3 | 4 | 3 | 7 | 0 | 17 | |
| | 2002 | 0 | 2 | 0 | 1 | 0 | 0 | 3 | |
| | 2003 | 0* | 0** | 1 | 2 | 1 | 0 | 4 | |
| | 2004 | 0* | 2** | 0 | 3 | 6 | 0 | 11 | |
| | 2005 | 0* | 0** | 1 | 1 | 1 | 0 | 3 | |
| | 2006 | 0* | 0** | 0 | 0 | 1 | 0 | 1 | |
| | 2007 | 0* | 1** | 0 | 0 | 1 | 0 | 2 | |
| | 2008 | 0* | 12** | 36 | 40 | 22 | 0 | 109 | |
| | 2009 | 0* | 1** | 2 | 4 | 4 | 0 | 11 | |
| | 2010 | - | - | - | - | - | - | 14 | |
| Hospitalisation | 1997 | 2 | 3 | 0 | 1 | 5 | 0 | 11 |  |
| | 1998 | 0 | 2 | 0 | 1 | 1 | 0 | 4 | |
| | 1999 | 2 | 45 | 34 | 11 | 9 | 0 | 101 | |
| | 2000 | 1 | 5 | 3 | 1 | 6 | 0 | 16 | |
| | 2001 | 1 | 0 | 0 | 0 | 3 | 0 | 4 | |
| | 2002 | 0 | 0 | 0 | 1 | 1 | 0 | 2 | |
| | 2003 | | | | | | | 2 | |
| | 2004 | | | | | | | 1 | |
| | 2005 | | | | | | | 1 | |
| | 2006 | | | | | | | 3 | |
| Isolates | 1997 | - | - | - | - | - | - | 36 |  |
| | 1998 | - | - | - | - | - | - | 17 | |
| | 1999 | - | - | - | - | - | - | 110 | |
| | 2000 | - | - | - | - | - | - | 30 | |
| | 2001 | - | - | - | - | - | - | 8 | |
| | 2002 | - | - | - | - | - | - | 4 | |
| | 2003 | - | - | - | - | - | - | 1 | |
| | 2004 | - | - | - | - | - | - | 5 | |
| | 2005 | - | - | - | - | - | - | 2 | |
| | 2006 | - | - | - | - | - | - | 1 | |
| | 2007 | - | - | - | - | - | - | 5 | |
| | 2008 | - | - | - | - | - | - | 24 | |

* Unknown age ** 0-4 years

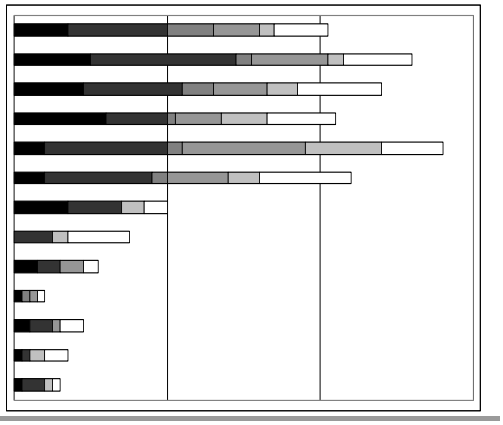
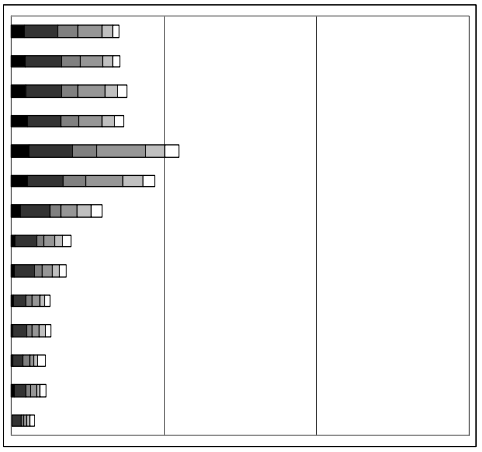
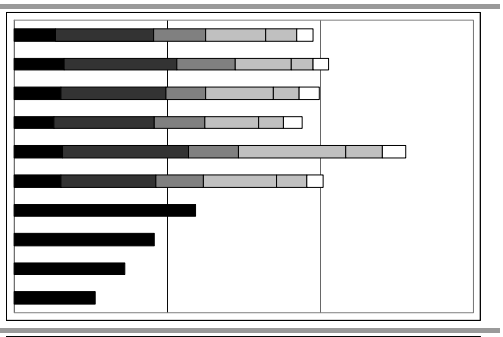
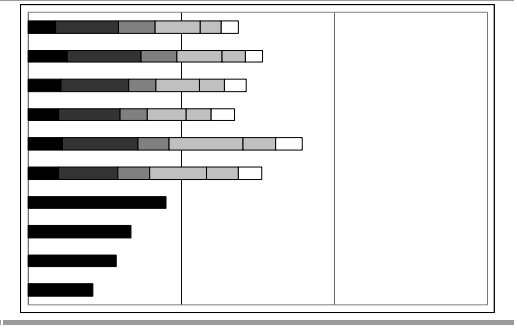
**Rubella (Acquired)** **ICD9 056.0, 056.7-9**

**ICD10 B06**

| | | Age (Years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **0** | **1-4** | **5-9** | **10-19** | **20-49** | **50+** | **Total** | N |
| Mortality | 1997 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
| | 1998 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 1999 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2002 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | |
| | 2003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2004 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2005 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | |
| | 2006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Notifications | 1997 | 0 | 8 | 6 | 1 | 4 | 0 | 19 |  |
| | 1998 | 0 | 5 | 7 | 0 | 6 | 0 | 18 | |
| | 1999 | 0 | 2 | 0 | 0 | 1 | 0 | 3 | |
| | 2000 | 0 | 1 | 4 | 0 | 7 | 0 | 12 | |
| | 2001 | 0 | 2 | 0 | 0 | 2 | 0 | 4 | |
| | 2002 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | |
| | 2003 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | |
| | 2004 | 0 | 4 | 11 | 28 | 10 | 0 | 39 | |
| | 2005 | 8 | 15 | 65 | 172 | 98 | 2 | 364 | |
| | 2006 | 0 | 1 | 0 | 0 | 4 | 1 | 11 | |
| | 2007 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | |
| | 2008 | 0 | 0 | 0 | 0 | 2 | 0 | 2 | |
| | 2009 | 0 | 0 | 0 | 4 | 2 | 1 | 7 | |
| | 2010 | - | - | - | - | - | - | 0 | |
| Hospitalisation | 1997 | 4 | 1 | 2 | 0 | 6 | 0 | 13 |  |
| | 1998 | 2 | 0 | 0 | 0 | 5 | 0 | 7 | |
| | 1999 | 0 | 1 | 0 | 0 | 7 | 0 | 8 | |
| | 2000 | 1 | 0 | 0 | 2 | 10 | 0 | 13 | |
| | 2001 | 1 | 0 | 0 | 0 | 6 | 0 | 7 | |
| | 2002 | 0 | 0 | 0 | 0 | 10 | 1 | 11 | |
| | 2003 | - | - | - | - | - | - | 2 | |
| | 2004 | - | - | - | - | - | - | 2 | |
| | 2005 | - | - | - | - | - | - | 9 | |
| | 2006 | - | - | - | - | - | - | 5 | |
| Isolates | 1997 | - | - | - | - | - | - | 11 |  |
| | 1998 | - | - | - | - | - | - | 13 | |
| | 1999 | - | - | - | - | - | - | 6 | |
| | 2000 | - | - | - | - | - | - | 4 | |
| | 2001 | - | - | - | - | - | - | 11 | |
| | 2002 | - | - | - | - | - | - | 13 | |
| | 2003 | - | - | - | - | - | - | 9 | |
| | 2004 | - | - | - | - | - | - | 20 | |
| | 2005 | - | - | - | - | - | - | 53 | |
| | 2006 | - | - | - | - | - | - | 21 | |
| | 2007 | - | - | - | - | - | - | 14 | |
| | 2008 | - | - | - | - | - | - | 16 | |

**Meningococcal disease** **ICD9 036.0-4, 036.8-9**

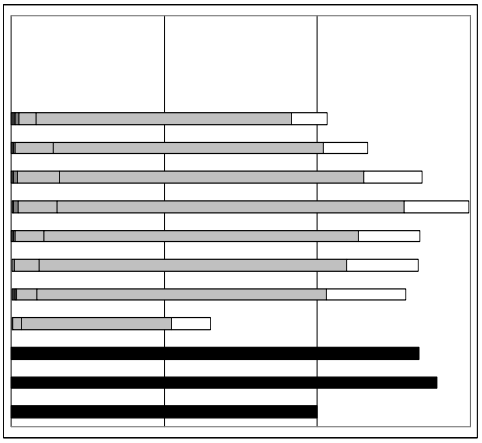
**ICD10 A39**

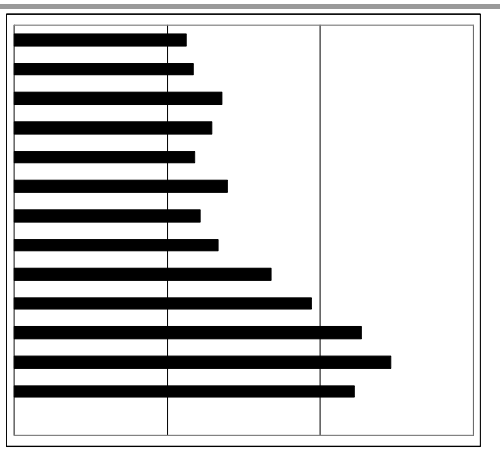
| | | Age (Years) | | | | | | | N |
|---|---|---|---|---|---|---|---|---|---|
| | | **0** | **1-4** | **5-9** | **10-19** | **20-49** | **50+** | **Total** | |
| Mortality | 1997 | 7 | 13 | 6 | 6 | 2 | 7 | 41 |  |
| | 1998 | 10 | 19 | 2 | 10 | 2 | 9 | 52 | |
| | 1999 | 9 | 13 | 4 | 7 | 4 | 11 | 48 | |
| | 2000 | 12 | 8 | 1 | 6 | 6 | 9 | 42 | |
| | 2001 | 4 | 16 | 2 | 16 | 10 | 8 | 56 | |
| | 2002 | 4 | 14 | 2 | 8 | 4 | 12 | 44 | |
| | 2003 | 7 | 7 | 0 | 0 | 3 | 3 | 20 | |
| | 2004 | 0 | 5 | 0 | 0 | 2 | 8 | 15 | |
| | 2005 | 3 | 3 | 0 | 3 | 0 | 2 | 11 | |
| | 2006 | 1 | 0 | 1 | 1 | 0 | 1 | 4 | |
| | 2007 | 2 | 3 | 0 | 1 | 0 | 3 | 9 | |
| | 2008 | 1 | 1 | 0 | 0 | 2 | 3 | 7 | |
| | 2009 | 1 | 3 | 0 | 0 | 1 | 1 | 6 | |
| Notifications | 1997 | 60 | 152 | 89 | 112 | 47 | 31 | 491 |  |
| | 1998 | 66 | 168 | 85 | 106 | 46 | 34 | 505 | |
| | 1999 | 66 | 166 | 75 | 124 | 56 | 44 | 531 | |
| | 2000 | 74 | 153 | 82 | 108 | 57 | 42 | 516 | |
| | 2001 | 82 | 200 | 111 | 222 | 91 | 64 | 770 | |
| | 2002 | 75 | 160 | 103 | 170 | 95 | 54 | 656 | |
| | 2003 | 42 | 137 | 50 | 74 | 63 | 49 | 415 | |
| | 2004 | 17 | 101 | 31 | 49 | 37 | 39 | 274 | |
| | 2005 | 14 | 94 | 33 | 47 | 33 | 30 | 251 | |
| | 2006 | 11 | 57 | 28 | 34 | 24 | 24 | 178 | |
| | 2007 | 7 | 63 | 25 | 32 | 30 | 25 | 182 | |
| | 2008 | 6 | 49 | 29 | 19 | 17 | 37 | 157 | |
| | 2009 | 13 | 55 | 20 | 28 | 16 | 28 | 160 | |
| | 2010 | - | - | - | - | - | - | 116 | |
| Hospitalisation | 1997 | 108 | 256 | 136 | 157 | 81 | 44 | 782 |  |
| | 1998 | 130 | 296 | 151 | 147 | 58 | 39 | 821 | |
| | 1999 | 123 | 274 | 104 | 176 | 67 | 53 | 797 | |
| | 2000 | 103 | 264 | 132 | 140 | 65 | 48 | 752 | |
| | 2001 | 127 | 329 | 130 | 280 | 97 | 60 | 1023 | |
| | 2002 | 122 | 249 | 123 | 191 | 80 | 42 | 827 | |
| | 2003 | - | - | - | - | - | - | 474 | |
| | 2004 | - | - | - | - | - | - | 367 | |
| | 2005 | - | - | - | - | - | - | 289 | |
| | 2006 | - | - | - | - | - | - | 211 | |
| Isolates (NRBM) | 1997 | 72 | 163 | 97 | 117 | 56 | 45 | 550 |  |
| | 1998 | 102 | 193 | 94 | 117 | 61 | 46 | 613 | |
| | 1999 | 86 | 176 | 71 | 114 | 65 | 57 | 570 | |
| | 2000 | 79 | 161 | 71 | 101 | 65 | 62 | 539 | |
| | 2001 | 90 | 196 | 82 | 193 | 86 | 69 | 716 | |
| | 2002 | 79 | 155 | 84 | 147 | 84 | 61 | 611 | |
| | 2003 | - | - | - | - | - | - | 361 | |
| | 2004 | - | - | - | - | - | - | 268 | |
| | 2005 | - | - | - | - | - | - | 229 | |
| | 2006 | - | - | - | - | - | - | 168 | |

**Hepatitis B** **ICD9 070.2-3**

**ICD10 B16 B17.0 B18.1**

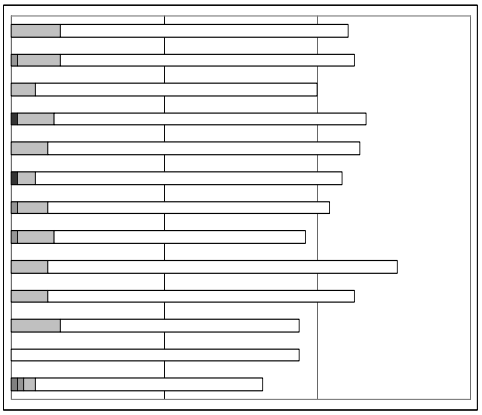
| | | Age (Years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **0** | **1-4** | **5-9** | **10-19** | **20-49** | **50+** | **Total** | N |
| Mortality (Acute) | 1997 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 1998 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 1999 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 4 | 4 | |
| | 2002 | 0 | 0 | 0 | 0 | 0 | 4 | 4 | |
| | 2003 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | |
| | 2004 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | |
| | 2005 | 0 | 0 | 0 | 0 | 1 | 4 | 5 | |
| | 2006 | 0 | 0 | 0 | 0 | 1 | 3 | 4 | |
| | 2007 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | |
| | 2008 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | |
| | 2009 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Notifications | 1997 | - | - | - | - | - | - | - | |
| | 1998 | - | - | - | - | - | - | - | |
| | 1999 | - | - | - | - | - | - | - | |
| | 2000 | 0 | 18 | 19 | 76 | 1167 | 165 | 1445 | |
| | 2001 | 1 | 8 | 9 | 174 | 1236 | 203 | 1631 | |
| | 2002 | 1 | 9 | 17 | 195 | 1390 | 269 | 1881 | |
| | 2003 | 2 | 10 | 19 | 178 | 1588 | 296 | 2093 | |
| | 2004 | 0 | 9 | 10 | 130 | 1440 | 280 | 1869 | |
| | 2005 | 0 | 5 | 8 | 114 | 1407 | 326 | 1860 | |
| | 2006 | 2 | 15 | 9 | 92 | 1322 | 365 | 1805 | |
| | 2007 | 0 | 5 | 2 | 40 | 685 | 180 | 912 | |
| | 2008 | 0 | 0 | 0 | 3 | 25 | 4 | 1865 | |
| | 2009 | 0 | 7 | 5 | 81 | 1519 | 424 | 1946 | |
| | 2010 | - | - | - | - | - | - | 1398 | |
| Isolates | 1997 | - | - | - | - | - | - | 787 | |
| | 1998 | - | - | - | - | - | - | 819 | |
| | 1999 | - | - | - | - | - | - | 950 | |
| | 2000 | - | - | - | - | - | - | 904 | |
| | 2001 | - | - | - | - | - | - | 827 | |
| | 2002 | - | - | - | - | - | - | 974 | |
| | 2003 | - | - | - | - | - | - | 849 | |
| | 2004 | - | - | - | - | - | - | 932 | |
| | 2005 | - | - | - | - | - | - | 1174 | |
| | 2006 | - | - | - | - | - | - | 1361 | |
| | 2007 | - | - | - | - | - | - | 1588 | |
| | 2008 | - | - | - | - | - | - | 1723 | |
| | 2009 | - | - | - | - | - | - | 1555 | |
| | 2010 | - | - | - | - | - | - | | |





**Pneumococcal disease** **ICD9 0382, 481, 4823, 485, ,486**

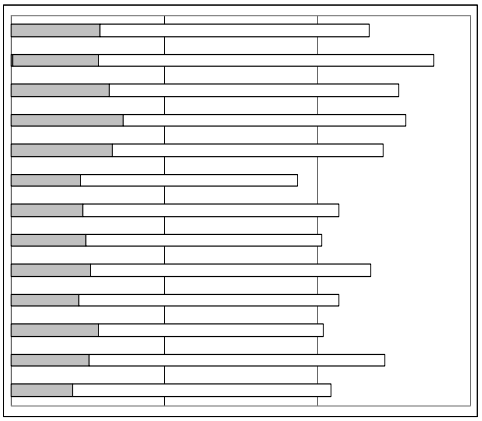
**ICD10 J13,18.0, 18.9,G00.1,A40.4**

| | | Age (Years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **0** | **1-4** | **5-9** | **10-19** | **20-49** | **50+** | **Total** | N |
| Mortality (J13) | 1997 | 0 | 0 | 0 | 0 | 8 | 47 | 55 |  |
| | 1998 | 0 | 0 | 0 | 1 | 7 | 48 | 56 | |
| | 1999 | 0 | 0 | 0 | 0 | 4 | 46 | 50 | |
| | 2000 | 0 | 1 | 0 | 0 | 6 | 51 | 58 | |
| | 2001 | 0 | 0 | 0 | 0 | 6 | 51 | 57 | |
| | 2002 | 0 | 0 | 0 | 0 | 3 | 50 | 54 | |
| | 2003 | 0 | 0 | 0 | 1 | 5 | 46 | 52 | |
| | 2004 | 0 | 0 | 0 | 1 | 6 | 41 | 48 | |
| | 2005 | 0 | 0 | 0 | 0 | 6 | 57 | 63 | |
| | 2006 | 0 | 0 | 0 | 0 | 6 | 50 | 56 | |
| | 2007 | 0 | 0 | 0 | 0 | 8 | 39 | 47 | |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 47 | 47 | |
| | 2009 | 0 | 0 | 1 | 1 | 2 | 37 | 41 | |
| Notifications | 1997 | - | - | - | - | - | - | - |  |
| | 1998 | - | - | - | - | - | - | - | |
| | 1999 | - | - | - | - | - | - | - | |
| | 2000 | - | - | - | - | - | - | - | |
| | 2001 | - | - | - | - | - | - | - | |
| | 2002 | - | - | - | - | - | - | - | |
| | 2003 | - | - | - | - | - | - | - | |
| | 2004 | - | - | - | - | - | - | - | |
| | 2005 | - | - | - | - | - | - | - | |
| | 2006 | - | - | - | - | - | - | - | |
| | 2007 | - | - | - | - | - | - | - | |
| | 2008 | 3 | 0 | 1 | 0 | 0 | 0 | 4 | |
| | 2009 | 10 | 31 | 3 | 0 | 0 | 0 | 44 | |
| | 2010 | - | - | - | - | - | - | 43 | |
| Isolates | 1997 | | | | | | | | |
| | 1998 | | | | | | | | |
| | 1999 | | | | | | | | |
| | 2000 | | | | | | | | |
| | 2001 | | | | | | | 249 | |
| | 2002 | | | | | | | 245 | |
| | 2003 | | | | | | | 232 | |
| | 2004 | | | | | | | 268 | |
| | 2005 | | | | | | | 234 | |
| | 2006 | | | | | | | 214 | |
| | 2007 | | | | | | | | |
| | 2008 | | | | | | | | |
| | 2009 | | | | | | | | |
| | 2010 | | | | | | | | |

**HPV** **ICD9**

**Age (Years)** **ICD10 C53**

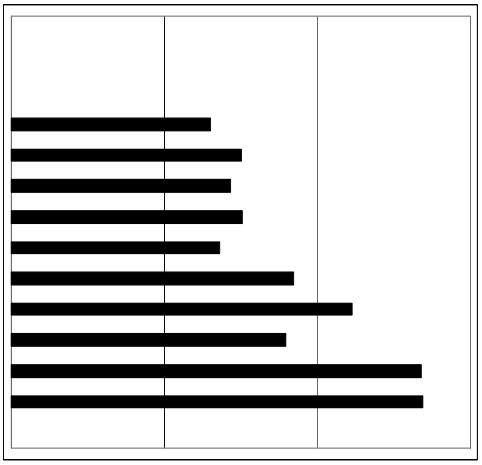
| | | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | Total |
|---|---|---|---|---|---|---|---|---|
| Mortality (C53) | 1997 | 0 | 0 | 0 | 0 | 58 | 176 | 234 |
| | 1998 | 0 | 0 | 0 | 1 | 56 | 219 | 276 |
| | 1999 | 0 | 0 | 0 | 0 | 64 | 189 | 253 |
| | 2000 | 0 | 0 | 0 | 0 | 73 | 185 | 258 |
| | 2001 | 0 | 0 | 0 | 0 | 66 | 177 | 243 |
| | 2002 | 0 | 0 | 0 | 0 | 45 | 142 | 187 |
| | 2003 | 0 | 0 | 0 | 0 | 47 | 167 | 214 |
| | 2004 | 0 | 0 | 0 | 0 | 49 | 154 | 203 |
| | 2005 | 0 | 0 | 0 | 0 | 52 | 183 | 235 |
| | 2006 | 0 | 0 | 0 | 0 | 44 | 170 | 214 |
| | 2007 | 0 | 0 | 0 | 0 | 57 | 147 | 204 |
| | 2008 | 0 | 0 | 0 | 0 | 51 | 193 | 244 |
| | 2009 | 0 | 0 | 0 | 0 | 40 | 169 | 209 |

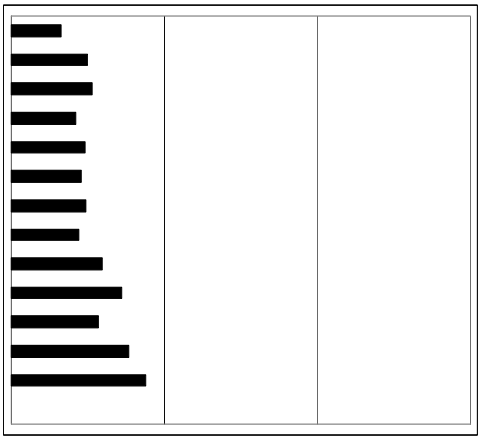


**Rotavirus** **ICD9**

**ICD10 -**

| | | Age (Years) 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | Total |
|---|---|---|---|---|---|---|---|---|
| Notifications | 1997 | - | - | - | - | - | - | - |
| | 1998 | - | - | - | - | - | - | - |
| | 1999 | - | - | - | - | - | - | - |
| | 2000 | - | - | - | - | - | - | 2864 |
| | 2001 | - | - | - | - | - | - | 3312 |
| | 2002 | - | - | - | - | - | - | 3160 |
| | 2003 | - | - | - | - | - | - | 3322 |
| | 2004 | - | - | - | - | - | - | 3000 |
| | 2005 | - | - | - | - | - | - | 4063 |
| | 2006 | - | - | - | - | - | - | 4903 |
| | 2007 | - | - | - | - | - | - | 3948 |
| | 2008 | - | - | - | - | - | - | 5895 |
| | 2009 | - | - | - | - | - | - | 5917 |
| | 2010 | - | - | - | - | - | - | - |
| Isolates | 1997 | - | - | - | - | - | - | 712 |
| | 1998 | - | - | - | - | - | - | 1094 |
| | 1999 | - | - | - | - | - | - | 1163 |
| | 2000 | - | - | - | - | - | - | 932 |
| | 2001 | - | - | - | - | - | - | 1067 |
| | 2002 | - | - | - | - | - | - | 1004 |
| | 2003 | - | - | - | - | - | - | 1079 |
| | 2004 | - | - | - | - | - | - | 975 |
| | 2005 | - | - | - | - | - | - | 1304 |
| | 2006 | - | - | - | - | - | - | 1585 |
| | 2007 | - | - | - | - | - | - | 1251 |
| | 2008 | - | - | - | - | - | - | 1691 |
| | 2009 | - | - | - | - | - | - | 1935 |
| | 2010 | | | | | | | |





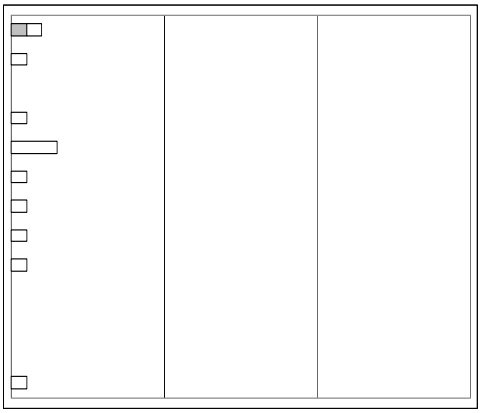
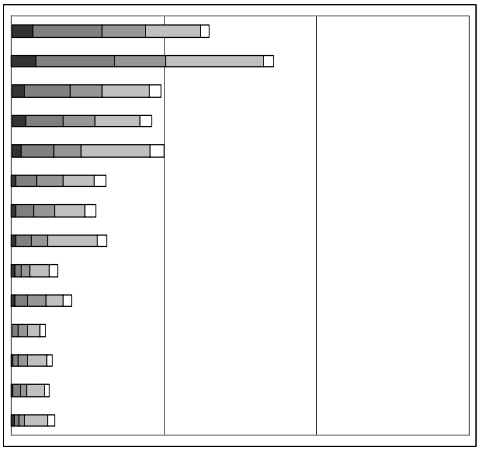
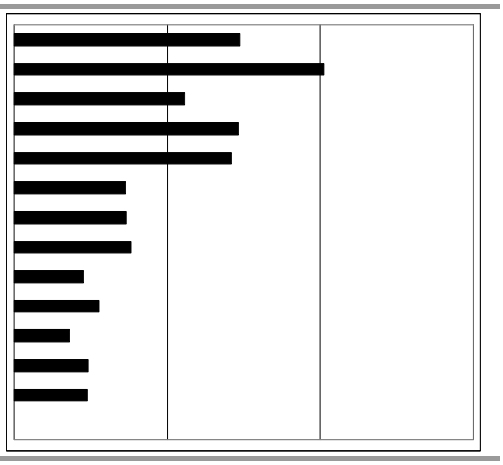
**Varicella** **ICD9 052**

**ICD10 B01**

| | | Age (Years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **0** | **1-4** | **5-9** | **10-19** | **20-49** | **50+** | **Total** | N |
| Mortality (B01) | 1997 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 1998 | 0 | 2 | 0 | 0 | 0 | 0 | 2 | |
| | 1999 | 0 | 0 | 0 | 2 | 1 | 1 | 4 | |
| | 2000 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | |
| | 2001 | 0 | 1 | 1 | 0 | 1 | 0 | 3 | |
| | 2002 | 2 | 0 | 0 | 0 | 1 | 1 | 4 | |
| | 2003 | 0 | 1 | 0 | 1 | 0 | 4 | 6 | |
| | 2004 | 0 | 1 | 0 | 0 | 0 | 3 | 4 | |
| | 2005 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| | 2006 | 0 | 0 | 1 | 0 | 1 | 1 | 3 | |
| | 2007 | 1 | 1 | 0 | 1 | 1 | 1 | 5 | |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2009 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| Notifications | 1997 | - | - | - | - | - | - | - | |
| | 1998 | - | - | - | - | - | - | - | |
| | 1999 | - | - | - | - | - | - | - | |
| | 2000 | - | - | - | - | - | - | - | |
| | 2001 | - | - | - | - | - | - | - | |
| | 2002 | - | - | - | - | - | - | - | |
| | 2003 | - | - | - | - | - | - | - | |
| | 2004 | - | - | - | - | - | - | - | |
| | 2005 | - | - | - | - | - | - | - | |
| | 2006 | - | - | - | - | - | - | - | |
| | 2007 | - | - | - | - | - | - | - | |
| | 2008 | - | - | - | - | - | - | - | |
| | 2009 | - | - | - | - | - | - | - | |
| | 2010 | - | - | - | - | - | - | - | |

**Hepatitis A** **ICD9**

**ICD10 B15**

| | | Age (Years) | | | | | | | N |
|---|---|---|---|---|---|---|---|---|---|
| | | **0** | **1-4** | **5-9** | **10-19** | **20-49** | **50+** | **Total** | |
| Mortality | 1997 | 0 | 0 | 0 | 0 | 1 | 1 | 2 |  |
| | 1998 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| | 1999 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | |
| | 2002 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| | 2003 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| | 2004 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| | 2005 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| | 2006 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2007 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 2009 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| Notifications | 1997 | 3 | 96 | 318 | 199 | 253 | 37 | 906 |  |
| | 1998 | 1 | 114 | 360 | 235 | 446 | 47 | 1203 | |
| | 1999 | 2 | 58 | 210 | 148 | 217 | 53 | 688 | |
| | 2000 | 3 | 63 | 174 | 146 | 205 | 54 | 645 | |
| | 2001 | 2 | 43 | 149 | 126 | 318 | 63 | 701 | |
| | 2002 | 0 | 22 | 97 | 119 | 144 | 51 | 433 | |
| | 2003 | 0 | 23 | 81 | 96 | 139 | 50 | 389 | |
| | 2004 | 1 | 21 | 69 | 76 | 227 | 45 | 439 | |
| | 2005 | 0 | 18 | 28 | 41 | 89 | 36 | 212 | |
| | 2006 | 0 | 17 | 59 | 85 | 78 | 38 | 277 | |
| | 2007 | 0 | 5 | 26 | 42 | 60 | 24 | 157 | |
| | 2008 | 0 | 6 | 26 | 43 | 88 | 26 | 183 | |
| | 2009 | 0 | 8 | 34 | 28 | 83 | 23 | 176 | |
| | 2010 | - | - | - | - | - | - | 171 | |
| Isolates | 1997 | - | - | - | - | - | - | 295 |  |
| | 1998 | - | - | - | - | - | - | 405 | |
| | 1999 | - | - | - | - | - | - | 223 | |
| | 2000 | - | - | - | - | - | - | 293 | |
| | 2001 | - | - | - | - | - | - | 284 | |
| | 2002 | - | - | - | - | - | - | 145 | |
| | 2003 | - | - | - | - | - | - | 146 | |
| | 2004 | - | - | - | - | - | - | 153 | |
| | 2005 | - | - | - | - | - | - | 91 | |
| | 2006 | - | - | - | - | - | - | 111 | |
| | 2007 | - | - | - | - | - | - | 72 | |
| | 2008 | - | - | - | - | - | - | 97 | |
| | 2009 | - | - | - | - | - | - | 96 | |
| | 2010 | - | - | - | - | - | - | - | |

# Appendix 2 Overview changes in the NIP since 2000

**Table A1 NIP 1st July 2001 – 31st August 2002**

(change: aP added at 4 years of age, for all children born on or after 1 January 1998)

| Age | Injection 1 | Vaccine 1 | Injection 2 | Vaccine 2 |
|---|---|---|---|---|
| 0-1 year* | DTwP-IPV | DTPw-IPV vaccine/NVI | Hib | Hib vaccine/NVI |
| 14 months | MMR | MMR vaccine/NVI | | |
| 4 years | DT-IPV | DT-IPV vaccine/NVI | **aP** | **Acellulair pertussis vaccine/GSK** |
| 9 years | DT-IPV | DT-IPV vaccine/NVI | MMR | MMR vaccine/NVI |

* 4 doses at 2, 3, 4 and 11 months, respectively

**Table A2 NIP 1st September 2002 – 28th February 2003**

(change: Men C added at 14 months of age, for all children born on or after 1 June 2001)*

| Age | Injection 1 | Vaccine 1 | Injection 2 | Vaccine 2 |
|---|---|---|---|---|
| 0-1 year** | DTwP-IPV | DTwP-IPV vaccine/NVI | Hib | Hib vaccine/NVI |
| 14 months | MMR | MMR vaccine/NVI | **Men C** | **NeisVac-C/Baxter** |
| 4 years | DT-IPV | DT-IPV vaccine/NVI | aP | Acellulair pertussis vaccine/GSK |
| 9 years | DT-IPV | DT-IPV vaccine/NVI | MMR | MMR vaccine/NVI |

* birth cohorts 01/06/1983-31/05/2001 were vaccinated in a catch-up campaign that started in June 2002
** 4 doses at 2, 3, 4 and 11 months, respectively

**Table A3 NIP 1st March 2003 – 31st December 2004**

(change: Hib given combined with DTwP-IPV at 2, 3, 4 and 11 months of age, for all children born on or after 1st April 2002*; and HBV added for infants in specified risk groups at 2, 4 and 11 months of age, for all children born on or after 1 January 2003)

| Age | Injection 1 | Vaccine 1 | Injection 2 | Vaccine 2 |
|---|---|---|---|---|
| 0-1 year** | **DTwP-IPV/Hib** | **DTwP-IPV/Hib vaccine/NVI** | **HBV*** ** | **HBVAXPRO/SP MSD** |
| 14 months | MMR | MMR vaccine/NVI | Men C | NeisVac-C/Baxter |
| 4 years | DT-IPV | DT-IPV vaccine/NVI | aP | Acellulair pertussis vaccine/GSK |
| 9 years | DT-IPV | DT-IPV vaccine/NVI | MMR | MMR vaccine/NVI |

* Indicated is the birth cohort from which children received at least one injection of the newly introduced vaccination
** 4 doses at 2, 3, 4 and 11 months respectively
*** Only children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for HBsAg

**Table A4 NIP 1st January 2005 – 31st December 2005**

(change: wP replaced by aP at 2, 3, 4 and 11 months of age, for all children born on or after 1 February 2004 )*

| Age | Injection 1 | Vaccine 1 | Injection 2 | Vaccine 2 |
|---|---|---|---|---|
| 0-1 year** | **DTaP-IPV/Hib** | **Infanrix IPV+Hib/GSK** | HBV*** | HBVAXPRO/SP MSD |
| 14 months | MMR | MMR vaccine/NVI | Men C | NeisVac-C/Baxter |
| 4 years | DT-IPV | DT-IPV vaccine/NVI | aP | Acellulair pertussis vaccine/GSK |
| 9 years | DT-IPV | DT-IPV vaccine/NVI | MMR | MMR vaccine/NVI |

* Indicated is the birth cohort from which children received at least one injection of the newly introduced vaccination
** 4 doses at 2, 3, 4 and 11 months respectively
*** Only children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for HBsAg

**Table A5 NIP 1st January 2006 – 31st May 2006**

(change: HBV added at birth for children of whom the mother tested positive for HBsAg; and Infanrix IPV+Hib/GSK replaced by Pediacel/SP MSD at 2, 3, 4 and 11 months, for all children born on or after 1 February 2005)*

| Age | Injection 1 | Vaccine 1 | Injection 2 | Vaccine 2 |
|---|---|---|---|---|
| At birth | **HBV**** | **HBVAXPRO/SP MSD** | | |
| 0-1 year*** | **DTaP-IPV-Hib** | **Pediacel/SP MSD** | HBV**** | HBVAXPRO/SP MSD |
| 14 months | MMR | MMR vaccine/NVI | Men C | NeisVac-C/Baxter |
| 4 years | DT-IPV | DT-IPV vaccine/NVI | aP | Acellulair pertussis vaccine/GSK |
| 9 years | DT-IPV | DT-IPV vaccine/NVI | MMR | MMR vaccine/NVI |

* Indicated is the birth cohort from which children received at least one injection of the newly introduced vaccination
** Only for children of whom the mother tested positive for HBsAg
*** 4 doses at 2, 3, 4 and 11 months respectively
**** Only children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for HBsAg

**Table A6 NIP from 1st June – July/August 2006**

(change: pneumococcal vaccination added at 2, 3, 4 and 11 months of age, for all children born on or after 1st April 2006; and introduction of combined vaccine DTaP-HBV-IPV/Hib at 2, 3, 4 and
11 months of age for children in specified risk groups born on or after 1st April 2006 [as a consequence a HBV vaccination at 3 months of age is added]).

**In general**

| Age | Injection 1 | Vaccine 1 | Injection 2 | Vaccine 2 |
|---|---|---|---|---|
| 0-1 year* | DTaP-IPV/Hib | Pediacel/SP MSD | **Pneumo** | **Prevenar/Wyeth** |
| 14 months | MMR | MMR vaccine/NVI | Men C | NeisVac-C/Baxter |
| 4 years | DT-IPV | DT-IPV vaccine/NVI | aP | Acellulair pertussis vaccine/GSK |
| 9 years | DT-IPV | DT-IPV vaccine/NVI | MMR | MMR vaccine/NVI |

* 4 doses at 2, 3, 4 and 11 months, respectively

**Specified risk groups**

| Age | Injection 1 | Vaccine 1 | Injection 2 | Vaccine 2 |
|---|---|---|---|---|
| At birth | HBV* | HBVAXPRO/SP MSD | | |
| 0-1 year** | **DTaP-HBV-IPV/Hib*** ** | **Infanrix hexa/GSK** | **Pneumo** | **Prevenar/Wyeth** |
| 14 months | MMR | MMR vaccine/NVI | Men C | NeisVac-C/Baxter |
| 4 years | DT-IPV | DT-IPV vaccine/NVI | aP | Acellulair pertussis vaccine/GSK |
| 9 years | DT-IPV | DT-IPV vaccine/NVI | MMR | MMR vaccine/NVI |

* Only for children born to mothers tested positive for HBsAg
** 4 doses at 2, 3, 4 and 11 months, respectively
*** Only children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for HBsAg

**Table A7 NIP from July/August 2006 – 31st December 2007**

(change: in July/August 2006 there was a transition from separate simultaneous DTP-IPV and aP vaccines to a combined formulation DTaP-IPV vaccine for children at 4 years of age born from July/August 2002 onwards. This DTaP-IPV vaccine replaces the DT-IPV given previously at 4 years of age; in September/October 2006 the MMR vaccine of NVI is replaced by MMR Vax of GSK and Priorix of SP MSD, for children born from July/August 2005 onwards)

**In general**

| Age | Injection 1 | Vaccine 1 | Injection 2 | Vaccine 2 |
|---|---|---|---|---|
| 0-1 year* | DTaP-IPV/Hib | Pediacel/SP MSD | Pneumo | Prevenar/Wyeth |
| 14 months | MMR | **MMR vaccine/NVI**<br>**Priorix/GSK**<br>**MMR VaxPro/SP MSD** | Men C | NeisVac-C/Baxter |
| 4 years | **DTaP -IPV** | **Triaxis Polio/SP MSD** | | |
| 9 years | DT-IPV | DT-IPV vaccine/NVI | MMR | MMR vaccine/NVI |

* 4 doses at 2, 3, 4 and 11 months, respectively

**Specified risk groups**

| Age | Injection 1 | Vaccine 1 | Injection 2 | Vaccine 2 |
|---|---|---|---|---|
| At birth | HBV* | HBVAXPRO/SP MSD | | |
| 0-1 year** | DTaP-HBV-IPV/Hib*** | Infanrix hexa/GSK | Pneumo | Prevenar/Wyeth |
| 14 months | MMR | **MMR vaccine/NVI**<br>**Priorix/GSK**<br>**MMR VaxPro/SP MSD** | Men C | NeisVac-C/Baxter |
| 4 years | **DTaP-IPV** | **Triaxis Polio/SP MSD** | | |
| 9 years | DT-IPV | DT-IPV vaccine/NVI | MMR | MMR vaccine/NVI |

* Only for children born to mothers tested positive for HBsAg

** 4 doses at 2, 3, 4 and 11 months, respectively

** Only children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for HBsAg

**Table A8 NIP from 1st January 2008 - September 2008**

(change: in 2008 the hepatitis B vaccination for children with Down syndrome born on or after 1 January 2008 is included in the NIP; and from July to mid-December 2008 Pediacel/SP MSD was replaced by Infanrix IPV+Hib/GSK at 2, 3, 4 and 11 months; and since February 2008 Infanrix IPV/GSK is also available for 4 year olds; and from September 2008 MMR vaccine/NVI is replaced by Priorix/GSK and from the end of October 2008 also by M-M-R VaxPro/SP MSD)

**In general**

| Age | Injection 1 | Vaccine 1 | Injection 2 | Vaccine 2 |
|---|---|---|---|---|
| 0-1 year* | DTaP-IPV/Hib | **Pediacel/SP MSD**<br>**Infanrix IPV+Hib/GSK** | Pneumo | Prevenar/Wyeth |
| 14 months | MMR | **MMR vaccine/NVI**<br>**Priorix/GSK**<br>**MMR VaxPro/SP MSD** | Men C | NeisVac-C/Baxter |
| 4 years | DTaP -IPV | Triaxis Polio/SP MSD*<br>**Infanrix IPV/GSK** | | |
| 9 years | DT-IPV | DT-IPV vaccine/NVI | MMR | **MMR vaccine/NVI**<br>**Priorix/GSK** |

* 4 doses at 2, 3, 4 and 11 months, respectively

** used until March 2008

**Specified risk groups**

| Age | Injection 1 | Vaccine 1 | Injection 2 | Vaccine 2 |
|---|---|---|---|---|
| At birth | HBV* | HBVAXPRO/SP MSD[1] | | |
| 0-1 year** | DTaP-HBV-IPV/Hib*** | Infanrix hexa/GSK | Pneumo | Prevenar/Wyeth |
| 14 months | MMR | **MMR vaccine/NVI**<br>**Priorix/GSK**<br>**MMR VaxPro/SP MSD** | Men C | NeisVac-C/Baxter |
| 4 years | DTaP-IPV | Triaxis Polio/SP MSD****<br>**Infanrix IPV/GSK** | | |
| 9 years | DT-IPV | DT-IPV vaccine/NVI | MMR | **MMR vaccine/NVI**<br>**Priorix/GSK** |

* Only for children born to mothers tested positive for HBsAg

** 4 doses at 2, 3, 4 and 11 months, respectively

*** Only children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for HBsAg

[1] HBVAXPRO/SP has been replaced temporarily by Engerix-B Junior due to delivery problems

**** used until March 2008

**Table A9 NIP from September2008 - 1st January 2010**

**In general**

| Age | Injection 1 | Vaccine 1 | Injection 2 | Vaccine 2 |
|---|---|---|---|---|
| 0-1 year* | DTaP-IPV/Hib | Pediacel/SP MSD<br>Infanrix IPV+Hib/GSK | Pneumo | Prevenar/Wyeth |
| 14 months | MMR | Priorix/GSK<br>MMR VaxPro/SP MSD** | Men C | NeisVac-C/Baxter |
| 4 years | DTaP -IPV | Infanrix IPV/GSK | | |
| 9 years | DT-IPV | DT-IPV vaccine/NVI | MMR | Priorix/GSK<br>MMR VaxPro/SP MSD** |

* 4 doses at 2, 3, 4 and 11 months, respectively
** in 2009 only MMRVaxPro is administered

**Specified risk groups**

| Age | Injection 1 | Vaccine 1 | Injection 2 | Vaccine 2 |
|---|---|---|---|---|
| At birth | HBV* | HBVAXPRO/SP MSD[1] | | |
| 0-1 year** | DTaP-HBV-IPV/Hib*** | Infanrix hexa/GSK | Pneumo | Prevenar/Wyeth |
| 14 months | MMR | Priorix/GSK<br>MMR VaxPro/SP MSD**** | Men C | NeisVac-C/Baxter |
| 4 years | DTaP-IPV | Infanrix IPV/GSK | | |
| 9 years | DT-IPV | DT-IPV vaccine/NVI | MMR | Priorix/GSK<br>MMR VaxPro/<br>SP MSD**** |

* Only for children born to mothers tested positive for HBsAg
** 4 doses at 2, 3, 4 and 11 months, respectively
*** Only children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for HBsAg
[1] HBVAXPRO/SP has been replaced temporarily by Engerix-B Junior due to delivery problems
**** in 2009 only MMRVaxPro is administered

**Table A10 NIP from 1st January 2010 onwards**

(change: in 2010 vaccination against human papilloma virus infection was introduced for 12-year old girls. This introduction was preceded by a catch up vaccination campaign for girls born in 1993-1996 in 2009)

**In general**

| Age | Injection 1 | Vaccine 1 | Injection 2 | Vaccine 2 |
|---|---|---|---|---|
| 0-1 year* | DTaP-IPV/Hib | Pediacel/SP MSD | Pneumo | Prevenar/Wyeth |
| 14 months | MMR | Infanrix IPV+Hib/GSK<br>MMR VaxPro/SP MSD | Men C | NeisVac-C/Baxter |
| 4 years | DTaP -IPV | Infanrix IPV/GSK | | |
| 9 years | DT-IPV | DT-IPV vaccine/NVI | MMR | MMR VaxPro/SP MSD |
| 12 years* | **HPV** | **Cervarix/GSK** | | |

* 4 doses at 2, 3, 4 and 11 months, respectively

** only girls were vaccinated and received 3 doses HPV vaccine at 0,1 and 6 months interval

**Specified risk groups**

| Age | Injection 1 | Vaccine 1 | Injection 2 | Vaccine 2 |
|---|---|---|---|---|
| At birth | HBV* | HBVAXPRO/SP MSD[1] | | |
| 0-1 year** | DTaP-HBV-IPV/Hib*** | Infanrix hexa/GSK | Pneumo | Prevenar/Wyeth |
| 14 months | MMR | MMR VaxPro/SP MSD | Men C | NeisVac-C/Baxter |
| 4 years | DTaP-IPV | Infanrix IPV/GSK | | |
| 9 years | DT-IPV | DT-IPV vaccine/NVI | MMR | MMR VaxPro/SP MSD |
| 12 years**** | **HPV** | **Cervarix/GSK** | | |

* Only for children born to mothers tested positive for HBsAg

** 4 doses at 2, 3, 4 and 11 months, respectively

*** Only children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for HBsAg

[1] HBVAXPRO/SP has been replaced temporarily by Engerix-B Junior due to delivery problems

**** only girls were vaccinated and received 3 doses HPV vaccine at 0,1 and 6 months interval

# Appendix 3 Composition of vaccines used in 2010

| Vaccine | Composition |
|---|---|
| **Pediacel/SP MSD** | Purified diphtheria toxoid > 30 IU |
| RVG 32118 | Purified tetanus toxoid > 40 IU |
| Diphtheria, tetanus, 5 component acellular | Purified pertussis toxoid (PT) 20 µg |
| vaccine, inactivated poliomyelitis vaccine | Purified filamentous haemagglutinin (FHA) 20 µg |
| and conjugated *Haemophilus influenzae* | Purified fimbrial agglutinogens 2 and 3 (FIM) 5 µg |
| type b-vaccin (adsorbed) | Purified pertactin (PRN) 3 µg |
| 0.5 ml | Inactivated type 1 poliovirus (Mahoney) 40 DU |
| | Inactivated type 2 poliovirus (MEF-1) 8 DU |
| | Inactivated type 3 poliovirus (Saukett) 32 DU |
| | *Haemophilus influenzae* type b polysaccharide |
| | (polyribosylribitol phosphate) 10 µg |
| | conjugated to tetanus toxoid (PRP-T) 20 µg |
| | absorbed to aluminium phosphate 1.5 mg |
| **DT-IPV vaccine/NVI** | Diphtheria-toxoid* > 5 IU |
| RVG 17641 | Tetanus toxoid* > 20 IU |
| Diphtheria (adsorbed), tetanus (adsorbed) a | Inactivated poliovirus type 1 > 40 DU |
| inactivated poliomyelitis vaccine | Inactivated poliovirus type 2 > 4 DU |
| 1 ml | Inactivated poliovirus type 3 > 7.5 DU |
| | *adsorbed to aluminium phosphate 1.5 mg Al3+ |
| **Prevenar/Wyeth** | Pneumococcal polysaccharide serotype 4* 2 µg |
| EU/1/00/167 | Pneumococcal polysaccharide serotype 6B* 4 µg |
| Pneumococcal saccharide conjugated | Pneumococcal polysaccharide serotype 9V* 2 µg |
| vaccine (adsorbed) | Pneumococcal polysaccharide serotype 14* 2 µg |
| 0.5 ml | Pneumococcal oligosaccharide serotype 18C* 2 µg |
| | Pneumococcal polysaccharide serotype 19F* 2 µg |
| | Pneumococcal polysaccharide serotype 23F* 2 µg |
| | *Conjugated to the CRM197 carrier protein and adsc |
| | aluminium phosphate 0.5 mg |
| **NeisVac-C/Baxter** | Neisseria meningitidis (C11-strain) |
| RVG 26343 | Polysaccharide O-deacetylated 10 µg |
| Conjugated meningococcal C saccharide | Conjugated to tetanus toxoid 10-20 µg |
| vaccine (adsorbed) | adsorbed to aluminium hydroxide 0.5 mg $Al^{3+}$ |
| 0.5 ml | |
| **HBVAXPRO/ SP MSD** | Hepatitis B-virus surface antigen, recombinant* HBs |
| EU/1/01/183 | Adsorbed to amorphe aluminiumhydroxyphosphatesu |
| Hepatitis B vaccine for children and | 0.25 mg |
| adolescents | *yeast strain *Saccharomyces cerevisiae* (2150-2-3) |
| 0.5 ml | |
| **Infanrix Hexa/GSK** | Adsorbed diphtheria toxoid > 30 IU |
| EU/1/00/152 | Adsorbed tetanus toxoid > 40 IU |
| Diphtheria, tetanus, pertussis (acellular | Adsorbed pertussis toxoid (PT) 25 µg |
| component), hepatitis B (rDNA), | Adsorbed filamentous haemagglutinin (FHA) 25 µg |
| inactivated poliomyelitis vaccine and | Adsorbed pertactin (PRN) 8 µg |
| conjugated *Haemophilus influenzae* type b- | Adsorbed recombinant HBsAg protein 10 µg |
| vaccine (adsorbed) | Inactivated type 1 poliovirus (Mahoney) 40 DU |
| 0.5 ml | Inactivated type 2 poliovirus (MEF-1) 8 DU |
| | Inactivated type 3 poliovirus (Saukett) 32 DU |
| | Adsorbed purified capsular polysaccharide of Hib (PR |
| | covalently bound to tetanus toxoid (T) 20-40 µg |

| | |
|---|---|
| **MMR Vax /SP MSD** | Mumps virus (Jeryl Lynn) > 5000 TCID50 (tissue cul |
| RVG 17672 | infectious doses) |
| Mumps, measles and rubella vaccine | Measles virus (Schwartz) > 1000 TCID50 |
| 0.5 ml | Rubella virus (Wistar RA 27/3) > 1000 TCID50 |
| **Infanrix IPV + Hib / GSK** | Adsorbed diphtheria toxoid > 30 IU |
| RVG 22123 / RVG 34567 | Adsorbed tetanus toxoid 20 - 40 IU |
| Diphtheria, tetanus, pertussis | Adsorbed pertussis toxoid (PT) 25 µg |
| (acellular component), inactivated | Adsorbed filamentous haemagglutinin (FHA) 25 µg |
| poliomyelitis vaccine and conjugated | Absorbed pertactin (PRN) 8 µg |
| *Haemophilus influenzae* type b-vaccine | Inactivated type 1 poliovirus (Mahoney) 40 DU |
| (adsorbed) | Inactivated type 2 poliovirus (MEF-1) 8 DU |
| 0.5 ml | Inactivated type 3 poliovirus (Saukett) 32 DU |
| | *Haemophilus influenzae* type b polysaccharide 10 µg |
| **Infanrix IPV / GSK** | Adsorbed diphtheria toxoid > 30 IU |
| RVG 34568 | Adsorbed tetanus toxoid > 40 IU |
| Diphtheria, tetanus, pertussis | Adsorbed pertussis toxoid (PT) 25 µg |
| (acellular component), inactivated | Adsorbed filamentous haemagglutinin (FHA) 25 µg |
| poliomyelitis vaccine | Absorbed pertactin (PRN) 8 µg |
| 0.5 ml | Inactivated type 1 poliovirus (Mahoney) 40 DU |
| | Inactivated type 2 poliovirus (MEF-1) 8 DU |
| | Inactivated type 3 poliovirus (Saukett) 32 DU |
| **M-M-R VaxPro / SP MSD** | Mumps virus (Jeryl Lynn) > 12,500 TCID50 (tissue c |
| EU/1/06/337/001 | infectious doses) |
| Mumps, measles and rubella vaccine | Measles virus (Enders' Edmonston) > 1000 TCID50 |
| 0.5 ml | Rubella virus (Wistar RA 27/3) > 1000 TCID50 |
| **Engerix-B Junior** | Hepatitis B-virus surface antigen, recombinant 10 µg |
| **Cervarix / GSK** | |

More extensive product information can be found at: www.cbg-meb.nl and www.emea.europe.eu.

**National Insitute for Public Health**
**and the Environment**
P.O. Box 1 | 3720 BA Bilthoven
www.rivm.com