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

The National Immunisation Programme in the Netherlands

Developments in 2011

RIVM report 210021015/2011

T.M. van 't Klooster et al.

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Colophon

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This investigation has been performed by order and for the account of Ministry of Health, Welfare and Sports, within the framework of V210021, Development future National Immunisation Programme.

Abstract

The National Immunisation Programme in the Netherlands
Developments in 2011

This report presents the developments of the National Immunisation Programme (NIP) in 2011, supported by updated surveillance data on current and potential target diseases. For many years, the participation level in the NIP has been high, which resulted in low incidences for most target diseases in 2011, i.e. diphtheria, tetanus, poliomyelitis, *Haemophilus influenzae* type b disease, rubella and meningococcal serogroup C disease. As in previous years, the NIP was effective and safe in the reporting period. Continuous monitoring is needed to further optimise the programme.

Pertussis, pneumococcal disease and meningococcal C disease
In 2010, the number of pertussis cases in young children was reduced due to the switch from whole-cell to acellular vaccine in 2005. The protective effect of the preschool booster introduced in 2001 at 4 years of age remained visible up to 13 years of age. In contrast, the incidence of pertussis has been increasing in adolescents and adults since 2004. The decrease in the number of cases of invasive pneumococcal disease (IPD) was caused by a decrease in the incidence of vaccine types in the vaccinated cohorts (87 percent in children < 2 years of age) and to a lesser extent in other age groups. However, this effect is partly counterbalanced by the increased incidence of non-vaccine types due to type replacement. On 1st March 2011, the 10-valent pneumococcal vaccine replaced the 7-valent vaccine. In 2009 and 2010, the first two cases of meningococcal group C disease in previously vaccinated persons were reported since the introduction of vaccination in 2002. Both persons had an immune disorder.

Hepatitis B
For hepatitis B the number of cases in 2010 was 8 percent lower than in 2009, mostly due to the decreasing number of acute HBV notifications in men who have sex with men (MSM). This suggests that the targeted vaccination programme introduced in 2002 has been effective. From birth cohort August 2011 onwards, a universal infant HBV vaccination has been included in the NIP.

Measles, mumps and human papillomavirus (HPV)
In Western Europe, the incidence of measles that increased in 2010 and 2011 reflected an increase in the number of imported cases in the Netherlands in 2011. The mumps outbreak that started among the highly vaccinated student population in late 2009, continued throughout 2010 and 2011. In 2011, interim vaccination coverage for three doses HPV vaccine in the first cohort of 12-year-old girls was 52.5 percent; the coverage among girls for the catch-up campaign increased from 47 percent to 52.3 percent.

Future candidates
With regard to potential new target diseases, it is noteworthy that the incidence of meningococcal serogroup B disease has further decreased every year since 2001. The incidence of rotavirus associated gastroenteritis, however, continued to rise in 2010. In 2010, the number of hepatitis A cases increased to the level of 2006 (1.6 cases per 100,000 inhabitants). For varicella and herpes zoster no striking changes occurred in 2010.

Safety
There were no unusual reports in the past year regarding the safety of the vaccines used in the NIP.

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

Rapport in het kort

Het Rijksvaccinatieprogramma in Nederland
Ontwikkelingen in 2011

Dit rapport geeft een overzicht van de mate waarin ziekteverwekkers uit het Rijksvaccinatieprogramma (RVP) in 2010 en 2011 voorkwamen. Daarnaast geeft het een overzicht van veranderingen in deze verwekkers, de gebruikte vaccins en bijwerkingen na vaccinatie. Hetzelfde geldt voor ontwikkelingen over nieuwe vaccins, die in de toekomst eventueel in het RVP worden opgenomen. De vaccinatiegraad is al vele jaren hoog, waardoor weinig mensen ziekten krijgen waartegen via het RVP wordt gevaccineerd (namelijk difterie, tetanus, polio, *Haemophilus inflluenzae* type b ziekte, rubella en meningokokken serogroep C). Ook in het onderzochte jaar blijkt het RVP effectief en veilig. Continue monitoring is nodig om het programma te optimaliseren.

Kinkhoest, pneumokokken en meningokokken C
In 2010 nam het aantal jonge kinderen met kinkhoest af, doordat het RVP in 2005 is overgegaan op een ander (acellulair) vaccin. Ook blijft het effect van de in 2001 toegevoegde booster op 4-jarige leeftijd zichtbaar tot en met 13 jaar. Wel neemt sinds 2004 het aantal adolescenten en volwassenen met kinkhoest toe. Het aantal mensen dat een pneumokokkenziekte kreeg, veroorzaakt door een type waartegen wordt gevaccineerd, is sterk afgenomen. Bij kinderen jonger dan 2 jaar is deze afname 87 procent. Bij de oudere leeftijdsgroepen was de daling minder door een toename van niet-vaccin typen. Per 1 maart 2011 is overgegaan op een pneumokokkenvaccin dat beschermt tegen tien typen in plaats van tegen zeven typen. In 2009 en 2010 zijn de eerste twee gevallen van meningokokken C gerapporteerd in gevaccineerde personen sinds deze vaccinatie in 2002 is geïntroduceerd. Beiden hadden een immuunziekte.

Hepatitis B
Het aantal gevallen met hepatitis B in 2010 is met 8 procent verminderd ten opzichte van 2009, voornamelijk doordat deze ziekte minder vaak is gemeld in mannen die seks hebben met mannen (MSM). Dit maakt aannemelijk dat het vaccinatieprogramma dat in 2002 voor deze groep is ingesteld, effectief is. Per 1 augustus 2011 krijgt iedereen die nadien is geboren de hepatitis B-vaccinatie.

Mazelen, bof en HPV
Mazelen kwam in 2010 en 2011 vaker voor in West-Europa, waardoor meer, doorgaans niet gevaccineerde, Nederlanders aldaar deze ziekte opliepen. De bofuitbraak in 2009 onder studenten, die daar doorgaans tegen zijn gevaccineerd, ging door in 2010 en 2011. De vaccinatiegraad (drie doses) voor de eerste groep 12-jarigen die tegen baarmoederhalskanker (HPV) zijn gevaccineerd was 52,5 procent in 2011; de vaccinatiegraad voor de inhaalcampagne onder 13- tot 16-jarigen steeg van 47 procent naar 52,3 procent.

Toekomstige kandidaten
Van de ziekten die in de toekomst mogelijk onder het RVP gaan vallen, komt meningokokken groep B sinds 2001 jaarlijks minder vaak voor. Maagdarminfecties veroorzaakt door Rotavirus neemt daarentegen verder toe in 2010 (naar 2180 ten opzichte van 1935 in 2009). In 2010 is het aantal hepatitis A-gevallen toegenomen tot het niveau van 2006 (1,6 gevallen per 100.000

inwoners). Voor waterpokken en gordelroos zijn geen grote veranderingen waargenomen in 2010.

Veiligheid
Er waren geen ongebruikelijke meldingen in het afgelopen jaar ten aanzien van de veiligheid van de vaccins binnen het Rijksvaccinatieprogramma.

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

Preface

This report gives an overview of the developments in 2011 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, 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. Moreover, 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. This report included also other meningococcal serogroups (i.e. non-serogroup B and C types) to enable studying the trends in these other serogroups. In addition, data on vaccines for infectious diseases tested in clinical trials and relevant for the Netherlands are included in this report.

The report is structured as follows: Chapter 1 gives short introduction, while in Chapter 2 surveillance methods, generally used to monitor the NIP, are described. Recent results on vaccination coverage of the NIP are discussed in Chapter 3. Chapter 4 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 5 describes new target diseases which might need consideration for the future NIP. Finally, in Chapter 6 vaccines for infectious diseases that are tested in clinical trials are described. In Appendix 2 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
AIDS	acquired immune deficiency syndrome
AlOH	Aluminum Hydroxide
AMC	Academic Medical Centre of Amsterdam
aP	acellular pertussis
AR	adverse reaction
a-VDPV	ambiguous vaccine-derived Polio viruses
BCG	Bacille Calmette Guérin
bOPV	bivalent oral polio vaccine
BPD	bronchopulmonary dysplasia
CBS	Central Bureau of Statistics
CD	*Clostridium difficile*
CDC	Centres for Disease Control and Prevention
CDI	*Clostridium difficile* infections
cGMP	current Good Manufacturing Practices
CHD	congenital heart disease
CI	confidence interval
CIb	Centre for Infectious Disease Control, the Netherlands
CIN	cervical intraepithelial neoplasia
CMR	Continuous Morbidity Registration
CMV	Cytomegalovirus
CSF	cerebrospinal fluid
CSI	Chlamydia Screening Implementation
c-VDPV	circulating vaccine-derived polio viruses
DTP	combination of diphtheria, tetanus, and pertussis vaccines
ECDC	European Centre for Disease Control and Prevention
EIA	Enzyme Immunoassay
ELISA	Enzyme-Linked ImmunoSorbent Assay
EMC	Erasmus Medical Centre Rotterdam
EU	European Union
FDA	U.S. Food and Drug Administration
FHA	Filamentous haemagglutinin
fHbp	factor H binding protein
GBS	Group B Streptococcus
GMC	geometric mean IgG concentrations
GP	General Practitioner
GSK	Glaxo Smith Kline
HBsAg	hepatitis B surface antigen
HAV	hepatitis A virus
HBV	hepatitis B virus
HBIG	hepatitis B immune globulin
HCV	hepatitis C virus
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus

HPV	human papillomavirus
hrHPV	high-risk Human papillomavirus
ICAAC	Interscience Conference on Antimicrobial Agents and Chemotherapy
ICD	International Classification of Diseases
ICER	Incremental cost effectiveness ratio
Ig	Immunoglobulin
IPCI	Interdisciplinary Processing of Clinical Information
IPD	Invasive pneumococcal disease
IPV	Inactivated polio vaccine
IU	International units
i-VDPV	VDPVs that can be attributed to an immuno-compromised person
LINH	Netherlands Information Network of General Practice
LIS	Laboratory of Infectious Diseases and Perinatal Screening
LMR	National Medical Registration
MenACWY-CRM	quadrivalent meningococcal CMR conjugate vaccine
MenACWY-TT	tetravalent meningococcal tetanus toxoid conjugate vaccine
MenA	Meningococcal serogroup A
MenB	Meningococcal serogroup B
MenC	Meningococcal serogroup C
MenCC	Meningococcal C conjugate vaccine
METC	Medical Ethics Review Committee
MHS	Municipal Health Service (GGD)
MLVA	multiple-locus variable number tandem repeat analysis
MMR	combination of measles, mumps, and rubella vaccines
MMRV	combination of measles, mumps, rubella, and Varicella vaccines
mOPV	monovalent oral polio vaccine
MPL	monophosphoryl lipid A
MRSA	Methicilline-resistant *Staphylococcus aureus*
MS	Multiple Sclerosis
MSM	men having sex with men
NadA	Neisserial adhesion A
NEW TBVAC	an EU consortium to develop an improved TB vaccine
NHBA	neisserial heparin binding antigen
NID	national immunisation day
NIP	national immunisation programme
NIVEL	Netherlands Institute for Health Services Research
NKR	The Netherlands Cancer Registry
NPL	National Polio Laboratory
NPG	National Influenza Prevention Programme
NRBM	Netherlands Reference laboratory for Bacterial Meningitis
NVI	Netherlands Vaccine Institute
OGZ	Public health

OMT	outbreak management team
OMV	outer membrane vesicle
OPV	oral polio vaccine
OroSCC	oropharyngeal squamous cell carcinoma
QALY	quality adjusted life years
Pa	*Pseudomonas aeruginosa*
PALGA	the nationwide network and registry of histo- and cytopathology in the Netherlands
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PIENTER	assessing immunisation effect to evaluate the NIP
PIM	pneumococcal vaccination trial
Pneumo	pneumococcal vaccination
Prn	Pertactin
PRN	plaque-reduction neutralisation
QALY	quality-adjusted life year
QC	quality control
R&D	research and development
RIVM	National Institute for Public Health and the Environment, the Netherlands
RSV	respiratory syncytial virus
SAE	serious adverse event
SES	social economic status
SHM	national database of the HIV treatment centres
SP-MSD	Sanofi Pasteur MSD
STI	sexually transmitted infections
TB	tuberculosis
Tdap	tetanus, diphtheria and pertussis vaccine
TIG	tetanus immune globulin
tOPV	trivalent oral polio vaccine
VAESCO	Vaccine Adverse Events Monitoring and Communication
VDPV	Vaccine-derived polio virus
VE	vaccine efficacy
VLP	Virus-Like Particle
VPD	vaccine preventable disease
VZV	varicella zoster virus
VUMC	VU University Medical Centre of Amsterdam
VWS	Ministry of Health, Welfare and Sport
WHO	World Health Organisation
wP	whole-cell pertussis
WP	work package
WPV	wild poliomyelitis virus
4CMenB	multicomponent meningococcal B vaccine

Summary

This report presents current vaccination schedules, surveillance data and scientific developments in the Netherlands for vaccine preventable diseases (VPDs) that are included in the National Immunisation Programme (NIP) (diphtheria, pertussis, tetanus, poliomyelitis, *Haemophilus influenzae* serotype b (Hib) disease, measles, mumps, rubella, meningococcal serogroup C disease, hepatitis B, pneumococcal disease and human papillomavirus (HPV)) and new potential target diseases for which a vaccine is available or might become available in the near future (rotavirus, varicella zoster virus (VZV), hepatitis A and meningococcal serogroups B and other serogroups (i.e. Y, W135, A, X, Z, 29E)).
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. As from 2010 onwards, vaccination against HPV is offered to 12-year-old girls.
New in 2011 is the replacement of the 7-valent pneumococcal vaccine for the 10-valent pneumococcal vaccine, which is offered to children born on or after 1st March 2011. Furthermore, vaccination against hepatitis B was introduced for all children born on or after 1st August 2011, for which the DTaP-HBV-IPV-Hib combination vaccine is used.
The average participation for all vaccinations (except for HPV) included in the NIP was considerably over 90%. The participation among schoolchildren for DT-IPV and MMR was with 92% somewhat lower than in the previous year, and for MMR below the WHO target of 95%. The interim immunisation coverage for three doses of HPV vaccination for adolescent girls was 52%.

Diphtheria
As in previous years, in 2010 and 2011 (up till week 32) no cases of diphtheria were reported.

Pertussis
In 2010, fewer pertussis patients were registered in the hospitalisation registration than in previous years. However, decline in coverage of hospitalisation data has to be taken into account. Furthermore, a real impact might be due to indirect protection of the booster for 4-year-olds and the switch from whole-cell to acellular vaccine. The switch from whole-cell to acellular vaccine has reduced the incidence of pertussis in young children. The protective effect of the preschool booster decreased over time but remained visible up to the age of 13, i.e. 9 years after the booster.
The disease incidence increased in adolescents and adults, which may pose a danger for infections in young children.

Tetanus
During 2010, two cases of tetanus in elderly, unvaccinated individuals occurred. Both survived. Based on cases occurring in 2011, there are indications that guidelines on post-exposure prophylaxis are not well implemented in clinical care.

Poliomyelitis
In 2010 and 2011 up till week 50, no cases of poliomyelitis were reported in the Netherlands. Europe has retained its polio-free status after a rapid (within 6

months) and successful interruption of circulation of wild poliovirus type 1, imported early 2010 from India into Tadjikistan with subsequent spread to at least three other countries (Uzbekistan, Kazakstan and Russia). No new cases have been reported in the WHO EURO Region since September 2010.
A phase I clinical trial assessing the safety and immunogenicity of an RIVM IPV-vaccine, containing attenuated Sabin strains, in adults in Poland is ongoing. The developed technology will be transferred to local vaccine manufacturers in low and middle-income countries.

***Haemophilus influenza* serotype b disease (Hib)**
There have been no significant changes in the number of invasive disease cases caused by *Haemophilus influenzae* serotype b (Hib) in 2010 (range 2006 to 2010: 24 to 38) in the Netherlands. The lower antibody titres (2006/2007 versus 1995/1996) in population-based sera in recently vaccinated infants 6-11 months of age need further study. It is important to note that after the booster dose at 11 months of age, no differences were found between the two study periods. Furthermore, numbers of Hib cases are low, i.e. infants with low antibody titers are likely to be protected by herd immunity.

Mumps
The mumps outbreak that started among students late 2009 continued in 2010 and 2011. The majority of cases (70%) had been fully (2*MMR) vaccinated. The mumps outbreaks are dominated by the genotype G5 mumps virus. Further studies are initiated in particular to investigate the transmission of mumps.

Measles
The incidence of measles in 2010 was 0.9/1,000,000 population (15 cases in total), which is just below the WHO elimination target (one per million). The largest cluster was of five cases, four of which were reported in December 2009. In the Western Europe, the incidence of measles increased in 2010 and 2011, and reflected in an increased number of imported cases in 2011.

Rubella
No cases of rubella were reported in the Netherlands in 2010. Novel laboratory strategies have been developed to enhance non-invasive sampling of patients (fingerprick blood/saliva) and differential serological screening of cases and clustered outbreaks for rubella.

Meningococcal serogroup C (MenC) disease
In 2009 and 2010, the first two cases of MenC disease in previously vaccinated persons were reported since the introduction of MenC vaccination in the Dutch NIP in 2002. However, both persons had an immune disorder. No significant changes in the properties of the MenC strains isolated from patients with invasive disease in the Netherlands have been observed.

Hepatitis B
In 2010, 191 cases of acute hepatitis B were reported in the Netherlands (incidence: 1.2/100,000 population), a decrease of 8% compared to 2009. Most of this decrease is due to a decreasing number of acute HBV cases reported in men who have sex with men (MSM). This suggests that the targeted vaccination programme is effective in reducing the incidence in this group. In both men and women, sexual contact remains the most frequently reported route of transmission for hepatitis B virus.
From birth cohort August 2011 onwards, universal infant HBV vaccination has been introduced in the Netherlands. HBV vaccine coverages for infants in the

targeted NIP programme were increasing in the past year. A main concern remains the completeness of the registration of infants born to HbsAg positive mothers in Præventis.

Pneumococcal disease
The introduction of vaccination against pneumococcal disease in the NIP 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.

Human papillomavirus (HPV)
Because the HPV vaccine was recently introduced, mainly vaccine data were presented. In 2011, interim vaccination coverage for the third dose in the first NIP cohort, i.e. girls born in 1997, was 52.5% (in 2012 the final coverage will be reported). In 2010, both the reporting rate of immediate occurring AEs (7.7 per 10,000 administered doses) as the reporting rate of spontaneous reported AEs (5.4 per 10,000 administered doses) was somewhat lower compared to 2009, in which a large HPV vaccination catch-up campaign was performed. In a questionnaire study, local reactions and systemic AEs were reported by 74-89% of the girls. No serious adverse events (SAE) that were considered causally related to the vaccination were reported.
Prior to vaccination, HPV DNA prevalence was estimated in the Netherlands in various studies to enable monitoring changes in HPV type distribution after vaccination. Vaccine types HPV16 and 18 were found in approximately a quarter of the HPV positive women.

Rotavirus
The rise in incidence of rotavirus associated gastroenteritis appears to continue in 2010. Rotavirus is the most important cause in case of hospitalisation due to gastroenteritis in children aged younger than 5 years. In 2010, G1P[8], G3P[8], and G2P[4] were most commonly found in the Netherlands.

Varicella zoster virus (VZV) infection
No striking changes occurred in the VZV epidemiology in the Netherlands in 2010. The seroprevalence measured in population-based sera in 2006/2007 was similar to that measured in 1995/1996, confirming the lower age of infection compared to other countries. This might be related to the lower disease burden as found for hospital admissions, which is further studied in GP-consultations.

Hepatitis A
In 2010, the number of hepatitis A infections (262 cases) increased to the level of 2006 (269 cases; 2007-2009: 156-189 cases/year). In Belgium, a country with comparable hepatitis A epidemiology, it was demonstrated that both universal and adult vaccination would not be economically attractive. This would imply that vaccination would have similar unfavourable cost-effectiveness ratios in the Netherlands.

Meningococcal serogroup B disease
The incidence of meningococcal B disease decreased further in 2010. A meningococcal B vaccine has been applied for a license (Bexsero, Novartis).

Men non-B and non-C
Since 2001 the number of patients with meningococcal serotype W135 disease has been decreasing. In 2010 the number of meningococcal serotype Y cases was 11. Serogroup Y has recently emerged in some countries.

Other possible future NIP candidates
Currently, two phase I vaccine trials against RSV infection in infants are running. Even if these trials would be successful, introduction of these vaccines to the market is not expected within the next five years.
Although the BCG (Tuberculosis) vaccine is effective in protecting infants against childhood forms of the disease, a more effective vaccine might improve the protection of adolescents and adults since BCG does not reliably prevent against pulmonary tuberculosis disease, the most common form of TB, in these age groups.
There is first concrete evidence, since the discovery of HIV in 1983, that a vaccine against HIV is potentially feasible.
At present no vaccine is available tot treat HCV infection. A number of approaches are currently under development.
Hospital-acquired infections are a major concern for public health in many industrialised countries and cause significant annual costs to the healthcare systems. Several companies are developing vaccines against *Clostridium difficile*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.
A conjugate vaccine against Group B Streptococcus (GBS) is currently in phase I/II clinical trials and CMV vaccines are under development.

Conclusion
The current Dutch NIP is effective and safe. To further optimise the programme, continuous surveillane and in-depth studies of both current and future target diseases are needed.

1 Introduction

T.M. van 't Klooster, H.E. de Melker

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* serotype b (Hib), meningococcal C disease (MenC), pneumococcal disease, human papillomavirus (HPV) and hepatitis B (HBV) is included in the programme. The vaccines that are currently administered and the age of administration are specified in Table 1 and Table 2. The 7-valent pneumococcal vaccine was replaced by the 10-valent pneumococcal vaccine for children born on or after 1st March 2011. Before 1st August 2011, HBV was included in the NIP only for children of whom at least one parent was born in a middle or high HBV endemic country, or the mother is HBV carrier (Table 1). HBV was included in the NIP for all children born on or after 1st August 2011 (Table 2). 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 other reports of the Cib, the Health Council and the KNCV Tuberculosis Foundation.[1-4] Besides HBV included in the NIP, a vaccination programme targeting groups at risk for HBV due to sexual behaviour or profession is in place in the Netherlands.

Table 1 Vaccination schedule of the NIP from 2006 to 1st August 2011

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	MenC
4 years	DTaP-IPV	DTaP-IPV	
9 years	DT-IPV	DT-IPV	MMR
12 years	HPV[c]	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/Onderwerpen/Onderwerpen/R/Rijksvaccinatieprogramma/De_inenting/Vaccinatieschema

Table 2 Vaccination schedule of the NIP from 1st August 2011 onwards

Age	Injection 1	Injection 2
2 months	DTaP-HBV-IPV/Hib	Pneumo
3 months	DTaP-HBV-IPV/Hib	Pneumo
4 months	DTaP-HBV-IPV/Hib	Pneumo
11 months	DTaP-HBV-IPV/Hib	Pneumo
14 months	MMR	MenC
4 years	DTaP-IPV	
9 years	DT-IPV	MMR
12 years	HPV[a]	

[a] Only for girls; three doses at 0 days, 1 month, 6 months.
Source:
http://www.rivm.nl/Onderwerpen/Onderwerpen/R/Rijksvaccinatieprogramma/De_inenting/Vaccinatieschema

The ultimate goal of the NIP is the eradication of all vaccine preventable diseases (VPDs) 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 and advise whether or not actions are needed to improve the NIP. Surveillance of the NIP consists of five pillars, as described in the following sections.

2 Surveillance methodology

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2.1 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.

2.1.1 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.

2.1.2 Morbidity data

2.1.2.1 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 have been enforced. Not all diseases targeted by the NIP were notifiable during the entire period. See Table 3 for more information.[5]

Table 3 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 required the 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.[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.

2.1.2.2 Hospital admissions

The National Medical Registration (LMR), managed by research institute Prismant, collects discharge diagnoses of all patients who are admitted to 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 has fluctuated 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, even though 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 more reliable source of surveillance.

2.1.3 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.

2.1.3.1 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 influenzae* diagnostics and typing are relevant for the NIP surveillance.

2.1.3.2 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 imply disease. Information on the number of tests done is not collected.

2.2 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.

2.3 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 (n_{blood}=10,128) and 2006-2007 (n_{blood}=7904) among 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.

2.4 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 at increased risk to one of the NIP target diseases. In the Netherlands, all vaccinations, administered within the framework of the NIP are registered in a central electronic (web-based) database on the individual level (Præventis).

2.5 Surveillance of adverse events following vaccination

From 1962 until 2011, RIVM was responsible for the safety surveillance of the NIP. An enhanced spontaneous reporting system for Adverse Events following Immunisation (AEFI) was combined with a telephone service for consultation and advice on schedules, contraindications, precautions, adverse events (AE) and other vaccination related problems. All incoming reports were accepted, irrespective of causal relation. After thorough validation and supplementation of the information, a (working) diagnosis was made and causality was assessed, based on international criteria (Table 4). As from 1st January 2011 the Netherlands Pharmacovigilance Centre (Lareb) has guided the enhanced spontaneous reports of AEs.

Table 4 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 was 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.

3 Vaccination coverage

E.A. van Lier

Just like previous years, at national level, the average participation for all vaccinations (except HPV) included in the NIP was considerably above the Dutch lower limit of 90% for 2011. The lower limit of 95%, set by the WHO as target for MMR vaccination, was not yet reached for schoolchildren (92%).
The above results are published in a report by the RIVM on the vaccination coverage in the Netherlands in 2011. The report included data on newborns born in 2008, toddlers born in 2005, schoolchildren born in 2000 and adolescent girls born in 1993-1997 (Table 5).[11]
For babies, the participation for the MMR, Hib and meningococcal C vaccination amounted to 96%, for the DTaP-IPV and pneumococcal vaccination to 95%. The participation for the first hepatitis B vaccination for children of mothers who are carrier of hepatitis B increased further to 99%. Besides, the participation among schoolchildren for DT-IPV and MMR was with 92% somewhat lower than in the previous year.
The interim immunisation coverage for three doses of HPV vaccination for adolescent girls born in 1997, who were offered HPV vaccination within the NIP for the first time, was 52.5% (in 2012 the final coverage will be reported). Within the HPV catch-up campaign (adolescent girls born in 1993-1996) a participation of 52.3% was reached.
Voluntary vaccination in the Netherlands results in a high vaccination coverage. High levels of immunisation are necessary in order to protect as many people individually as possible, and for most target diseases in the NIP also to protect the population as a whole (group immunity) against outbreaks. 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 5 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
2011	2008	95.4	96.0	94.8	95.9	95.9	2005	92.0	2000	92.2	92.1

	Newborns*		
Report Year	**cohort**	**HBV[a]**	**HBV[b]**
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
2011	2008	94.8	96.6

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

** Only for newborns born on or after 1st 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

4 Current National Immunisation Programme

4.1 Diphtheria

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4.1.1 Key points

- In 2010-2011, no cases of diphtheria were reported in the Netherlands.

4.1.2 Changes in vaccine 2010-2011-2012

In 2011, infants born before 1st August received Pediacel (SP-MSD) and till then only infants at risk for Hepatitis B received Infanrix Hexa (GSK). In accordance with the recommendation of the Health Council regarding universal vaccination against Hepatitis B[12], from August onwards all infants received Infanrix Hexa (GSK). At the age of 4, Infanrix-IPV (GSK) was used as a preschool booster throughout the whole period. 9-year-old children received dT-IPV (NVI).

4.1.3 Epidemiology

In 2010 and in 2011 up till week 32 no diphtheria notifications were received.[13]

4.1.4 Pathogen

In July 2011, two strains suspected of causing skin-diphtheria were sent to the RIVM; both were diphtheria-toxin-PCR negative. The first case, a 20-year-old man with a wound on the right foot had visited a hospital in the Philippines. The travelling history of the other case, a 25-year-old woman with a wounded toe, was unknown. She had an anti-diphtheria antibody titer of 0.1 IU/ml and was therefore protected according to the WHO standard.

4.1.5 Adverse events

Two studies showed that diphtheria-tetanus-toxoid vaccine is well tolerated in adults who more than 10 years before[14] or never[15] received a diphtheria-tetanus-pertussis (DTP) vaccination.

4.1.6 Current/ongoing research

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

4.1.7 International developments

No relevant international developments have occurred in 2010 and 2011.

4.2 Pertussis

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4.2.1 Key points

- In 2010, according to the hospital registration, only 94 patients were hospitalised for pertussis. This is the lowest number in the last 15 years; increased underreporting of hospital registration has to be taken into account.

- The protective effect of the preschool booster remained visible up to the age of 13, i.e. 9 years after the booster dose.
- The switch from whole-cell to acellular vaccine has reduced the incidence of pertussis in young children.
- Since 2005 the pertussis incidence in infants, aged 0-4 years, shows a decreasing trend. This is probably due to indirect protection of the booster for 4-year-olds and the switch from whole-cell to acellular vaccine.
- Despite this improved impact in younger children, disease incidence increased in adolescents and adults.

4.2.2 Changes in vaccine 2010-2011-2012

See paragraph 4.1.2.

4.2.3 Epidemiology

4.2.3.1 Disease

Since the sudden upsurge of pertussis in 1996[16], the incidence of reported and hospitalised pertussis cases has remained high. Peaks in reported cases are observed every two to three years. In 2009 and 2010 incidences were lower compared with 2007 and 2008. Following the trends in the previous years, this may suggest an increase will occur in 2011. According to the hospital registration, in 2010 hospitalised pertussis cases were the lowest in the last 15 years (n=94) (Figure 1). The coverage of the hospital registration has decreased since 2005.

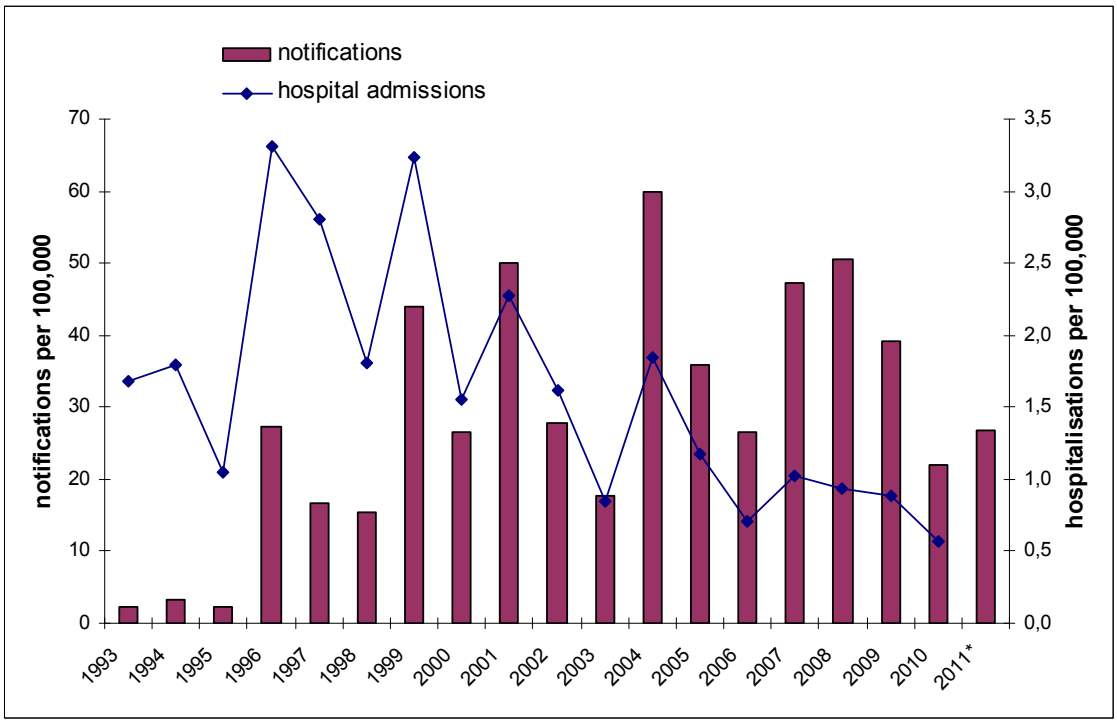

Figure 1 Incidence of pertussis notifications (bars) and hospitalisations (line) by year in 1993 to 2011.
**Notifications in 2011 were available until July and extrapolated to a whole year. Data for hospitalisations were not yet available for 2011.*

The last decade, several measures were undertaken to protect the youngest infants, who are most at risk for severe pertussis.[17] In January 1999, an accelerated schedule was introduced in which the first three vaccinations were given at the ages of 2, 3 and 4 months instead of 3, 4 and 5 months. Furthermore, from November 2001 onwards, an acellular pertussis booster dose at 4 years of age was added to the NIP for children. Finally, in January 2005 an infant DTaP-IPV-Hib vaccine, containing acellular pertussis components, replaced the whole-cell combination vaccine. This had a positive effect on the incidence of pertussis notifications in young children, lasting until the age of 4 years, when the booster dose is offered (Figure 2). It can be seen that the incidence in children, born since 2005 (yellow tinted bars), has decreased compared with children born before 2005. Also in the first cohort of children eligible for booster vaccination (6 years in 2011) a decrease compared to previous introduction of booster vaccination was visible. However, the administration of the booster dose at 4 years of age hampers a good evaluation of the continuation of the effect of the acellular primary series.

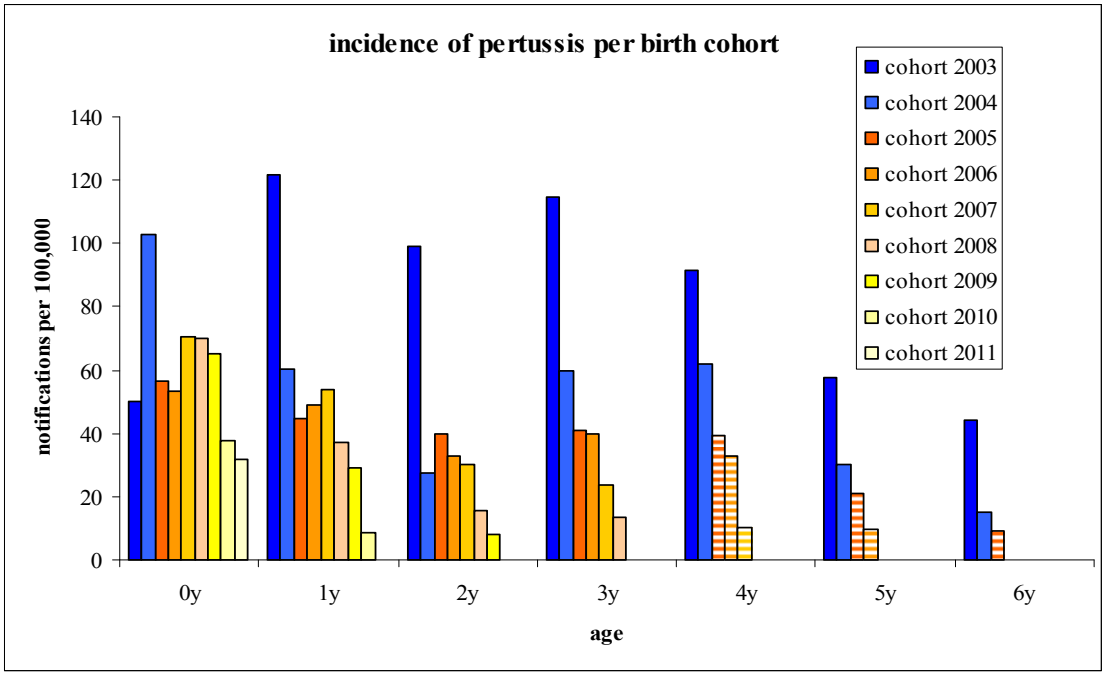

Figure 2 The effect of the switch from whole-cell to acellular vaccine.
*Incidence of pertussis notifications by age for children born in 2003-2004 (blue bars: vaccinated with the whole-cell vaccine) and children born in 2005-2011 (yellow tinted bars: vaccinated with acellular vaccine). The striped bars indicate children eligible for both the infant acellular combination vaccine and the acellular booster dose at 4 years of age. *Notifications in 2011 were extrapolated to a whole year.*

The booster dose at 4 years of age has led to a decrease in the incidence of pertussis notifications in the age groups eligible for this vaccination. The positive effect of the booster remained visible in 13-year-olds, i.e. 9 years after the booster. However, continued surveillance is needed to determine if the positive effect of the booster will sustain in more epidemic years (Figure 3).

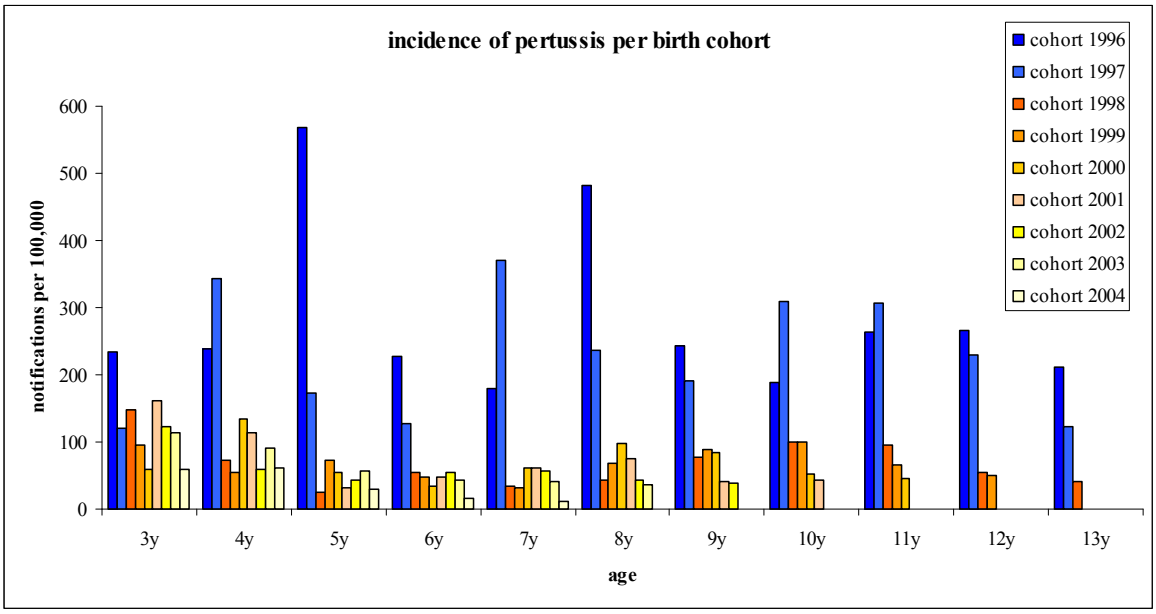

Figure 3 Effect of the booster for four year-olds.
*Incidence of pertussis notifications by age for children born in 1996-1997 (blue bars: not eligible for the acellular vaccine booster vaccination) and children born in 1998-2004 (yellow bars: eligible for the acellular booster vaccination). *Notifications in 2011 were extrapolated to a whole year.*

The positive impact of these measures is also visible in the hospitalisation rates of infants up till 3 years of age. (Figure 4) However, in this case we must bear in mind that the coverage of participating hospitals has decreased to ≈ 80%-90% since 2005. Because the number of hospitalisations is very small, it is difficult to calculate the effect of decreasing coverage properly.
Therefore, the decrease is hospitalisation rate can also (partly) be a result of decreased coverage.

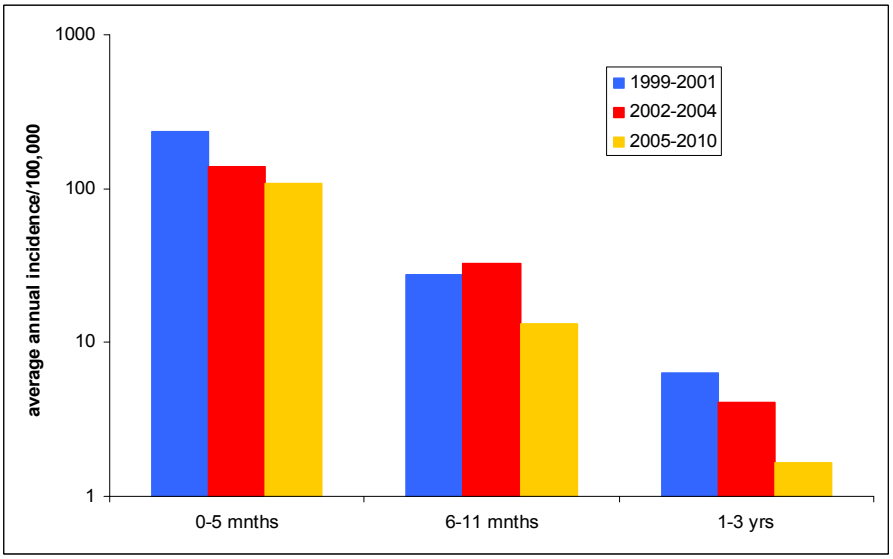

Figure 4 Average annual incidence (log-scale) of children hospitalised for pertussis by age group and per period 1999-2001 (no preschool booster), 2002-2004 (preschool booster given to 4-year-olds) and 2005-2010 (acellular vaccine in use).

Despite these positive findings in younger children, the incidence in adolescents and adults show an increasing trend (Figure 5).

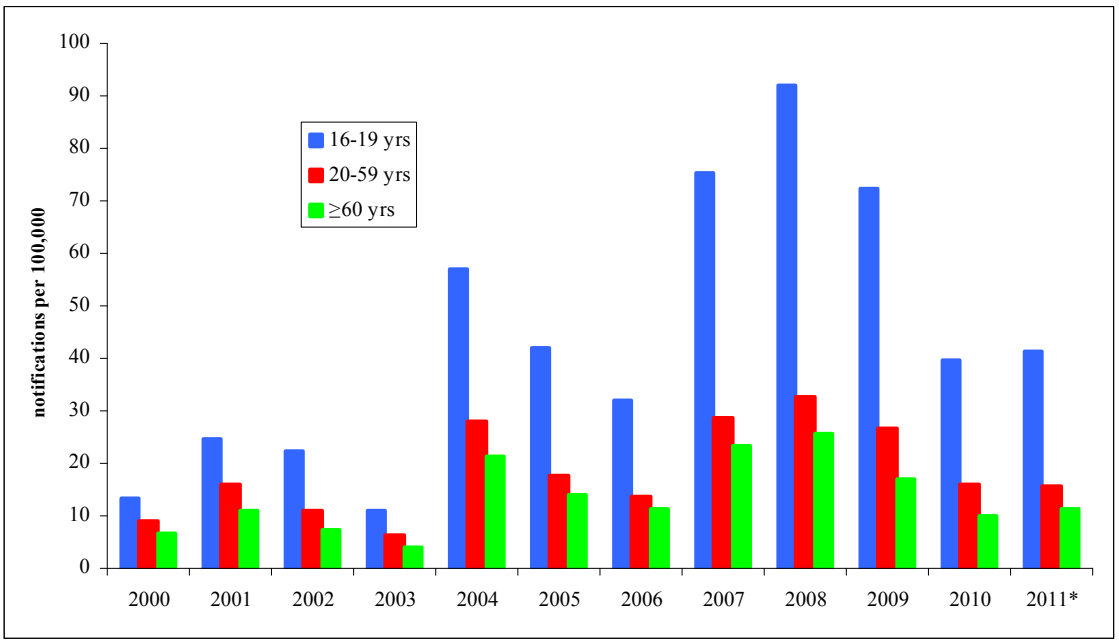

*Figure 5 The incidence in adolescents and adults is still increasing. Incidence of pertussis notifications for the age categories 16-19, 20-59 and ≥ 60 years. *Notifications in 2011 were extrapolated to a whole year.*

4.2.3.2 Vaccine effectiveness

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

VE (%) = 1- [PCV / (1-PCV) * (1-PPV/PPV].
PCV = proportion of cases vaccinated, PPV = proportion of population vaccinated, and VE = vaccine efficacy.

For some age groups, the proportion of vaccinated cases exceeded the estimated vaccine coverage of the population (96% for infant vaccinations and 92% for booster dose in 4-year-olds). 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. After the introduction in 2005 of an infant combination vaccine with acellular pertussis components, the VE for children aged 1-3 years has increased, perhaps due to a better protection of this group by the acellular vaccine compared to the previously used whole-cell vaccine.

Table 6 Estimation of pertussis vaccine effectiveness of the primary series of infant vaccinations by the 'screening method' for 1- to 3-year-olds per year

Age	'93	'94	'95	'96	'97	'98	'99	'00	'01	'02	'03	'04	'05	'06	'07	'08	'09	'10
1yr	94	77	92	32	29	38	63	78	73	63	29	54	72	87	92	90	90	97
2yr	92	58	42	63	-	33	22	52	46	41	-	-	67	58	92	91	89	93
3yr	94	79	60	38	-	9	-	-	-	54	10	37	59	43	84	82	83	89

As already mentioned, an acellular booster was implemented in November 2001 for children born in 1998. Since then vaccines from different providers have

been used, each containing a different number and dose of pertussis antigens. As shown in Table 7, vaccine effectiveness of the preschool booster decreases with age, suggesting waning immunity. Continued surveillance is necessary to monitor the impact of these changes in vaccine products on long term vaccine effectiveness.

Table 7 Estimation of pertussis vaccine effectiveness of the preschool booster by the 'screening method' for 6- to 11-year-olds per year

Age	'04	'05	'06	'07	'08	'09	'10
5yr	77	71	82	86	80	84	83
6yr	74	70	80	79	71	61	89
7yr		68	57	68	71	51	61
8yr			67	75	56	47	35
9yr				73	63	36	49
10yr					60	-	13
11yr						-	11
12yr							45

4.2.4 *Pathogen*

As observed in previous years, P3 *Bordetella pertussis* strains predominated in 2011. 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.[18] P3 strains may be more fit when a large fraction of the host population is primed (by vaccination), as pertussis toxin is known to suppress both the innate and adaptive immune system.[19, 20] Like the P1 strains, P3 strains show (small) differences in antigenic make-up in pertussis toxin and pertactin compared to pertussis vaccines.[21] 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 2011. The relevance of this shift in serotype is not clear. Strains which do not produce one or more vaccine components, in particular pertactin (pertactin knock-out strains), have been identified in France, Japan and Sweden[22, 23] (unpublished data the Netherlands). In 2011, pertactin knock-out strains were first identified in the Netherlands, comprising 8% of the population. Currently used acellular vaccines all contain pertactin, and it seems reasonable to assume that they are less effective against pertactin knock-out strains.

4.2.5 *Adverse events*

The enhanced passive surveillance system, until December 2010 in place at CIb, receives reports of Adverse Events Following Immunisation (AEFI), for all vaccines included in the NIP. In 2010, reports following infant doses of DTaP-IPV-Hib, scheduled at 2, 3, 4 and 11 months, amounted to 47% (n=651) of the total number of reports. Except for 14 children, all children received PCV7 simultaneously and 19% received also (combined) hepatitis B vaccine (n=125). The number of reports in 2010 is within the range of the number of reports in the time-period 2005-2009 (i.e. 593-756).
The reporting rate of adverse events (AE) per 1000 vaccinees for infants (at 2, 3, 4 and 11 months) was similar to 2005-2009, amounting to 3.8 and 3.7 per 1000 vaccinated infants. For the third consecutive year, both in absolute number and reporting rate, AE after the DTaP-IPV booster vaccination at 4 years of age

were most frequent (n=313, 1.3/1000 vaccinees), mainly concerning local reactions with or without fever.[24]

From the second half of 2008 onwards, (nearly) all children receiving the 4 yr booster DTaP-IPV vaccination at 4 years of age had infant vaccination with acellular DTP-IPV-Hib vaccine. In a cross-section study, we found that the frequency of AEs after DTaP-IPV booster immunisation in 4–year-old children is higher in children primed with DTaP-IPV-Hib than in children primed with DTwP-IPV-Hib.[25] This higher risk on local reactions and fever after booster doses of acellular pertussis DTP-IPV in aP primed children compared to wP primed children is also described in the literature.[26-28] Therefore, the use of vaccines with reduced antigens, which may decrease the reactogenicity of booster vaccination, needs to be explored. Alternatively, spacing between the booster and primary series might lead to a decrease in AEs.

In the literature, three recent studies assessed the safety of combined DTaP-IPV vaccines for primary vaccination. Both vaccines (DTaP-IPV;Tetraxim and DTaP-IPV/PRP-T;Pentaxim, respectively) had a good safety profile.[29-31]
Andrews et al. confirmed that the change from DTwP-Hib vaccine to the DTaP-Hib-IPV vaccine in infancy improved the reactogenicity profile documented in clinical trials with this vaccine, and resulted in a significant reduction in the frequency of medically attended AEs in the immediate post-vaccination period.[32]
Booy et al. showed that a decennial booster dose of reduced antigen content dTaP vaccine was well tolerated in adults.[33] This was also found during a mass vaccination campaign of healthcare personnel less than two years following previous tetanus vaccination.[34] In addition, a phase IV trial showed that a second low dose DTaP-IPV booster in adolescents was well tolerated.[35]

4.2.6 Current/ongoing research

The prevalence of pertactin knock-out mutants, and other mutants which do not produce one or more 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 or the vaccination schedule 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.
In the MEMORY study the long term protection against pertussis in different groups of children 3, 4, 6 and 9 years of age is studied with a special focus on cellular immunity. Three years after the wP or aP vaccinations in the first year of life and two to five years after the aP-booster vaccination low IgG levels to the pertussis vaccine proteins were found. At the same time, however, in about 70% of these children, pertussis protein-specific memory B-cells were identified.[36]
After the preschool booster, aP primed children showed high pertussis protein-specific IgG levels and high numbers of memory B-cells. Also, the quantity and the quality of the antibody response after the aP-booster in the 4-year-old children was found to be dependent on the doses of the booster vaccine and on the vaccination history of the children. A high dose resulted in higher responses

compared with the low dose and aP-primed children responded better than wP-primed children.[37] The vaccination history seems also to determine the IgG-subclass distribution elicited after a secondary antibody response either induced by pertussis booster vaccination or infection. Although IgG1 was the predominant subclass for all pertussis antigens in both healthy and infected children, elevated IgG4 levels were only present in children who had received repeated numbers of acellular pertussis vaccinations. The pronounced anti-pertussis IgG4 response might reflect the Th2-skewing of the immune response after aP vaccination.[38] As yet the consequences are not clear, but a Th2 skewed immune system has been associated with a higher risk on allergic and auto-immune manifestations.

In addition to the human studies, the effect of *B. pertussis* pathogen adaptation on the efficacy of existing pertussis vaccines and vaccine candidates is studied in animal models. Changes in pathogenesis and protection are studied in the coughing rat model and/or mouse intranasal challenge model. This research may provide clues for improving existing pertussis vaccines and/or contribute to the development of a new generation of pertussis vaccines.

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.

Because most infants with pertussis are infected by their parents, the number of pertussis cases in young infants can be further decreased by vaccination of the parents, as shown by De Greeff et al.[39] Currently, we are analysing the cost-effectiveness of this ‘cocooning strategy’.

Preliminary results of a cost-effectiveness analysis of the 'cocooning'-strategy, i.e. vaccinating mothers and/or fathers of newborns, show that costs related to this preventive measure exceed the benefits of disease prevention. Therefore, 'cocooning' will probably not be cost-effective.

4.2.7 International developments

At the last Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) Witt et al. presented results of a study on vaccine effectiveness of an acellular pertussis booster vaccination during an outbreak of pertussis. They concluded that acellular boosters became ineffective within three years after immunisation.[40] In is not in line with our findings, but our findings on vaccine effectiveness are very crude and not determined during an outbreak.

Currently, a collaborative study of the Medical Research Council (MRC) of Gambia and RIVM is performed. Seroprevalence of pertussis by age will be assessed making use of stored Keneba Manduar cohort samples. Then existing cord blood samples from the Sukuta cohort will be studied to assess the role of maternal immunity, which is essential information for the design of strategies to better protect not yet (fully) vaccinated infants. Finally, clinical isolates will be collected and characterised to enable comparison to vaccine strains, to determine if escape variants have arisen as observed elsewhere, which is essential information to guide vaccination policy and understand the cause of outbreaks.

In collaboration with the Sanger Centre (Cambridge UK) and 12 other countries we participate in a project which aims to study the global epidemiology and

evolution of *B. pertussis*. For this project, the genome of about 400 *B. pertussis* strains will be sequenced. At the European level we are members of the EUperstrain group, which focuses on the lab surveillance of pertussis. This group reports on the strains circulating in Europe every two to three years. Together with a number of other European partners, we have obtained an ECDC grant (~€ 800,000) to setup a European wide lab surveillance for pertussis. In this setting, LIS is responsible for strain surveillance and genomics.

The Cib has set up a website (MLVA.net) for typing of *B. pertussis* which is currently being used by groups from China, Japan, Australia, US, Russia and several European countries.

The EU project Child-Innovac, performing a first-in man (phase I) study with a new generation live attenuated *B. pertussis* vaccine, in which RIVM participates by developing knowledge and tools regarding pertussis specific memory immunity in children, is coming to a close. Results will be important to guide policy discussions on vaccine innovation and to be able to step into new research consortia or immuno-clinical studies.

4.3 Tetanus

S.J.M. Hahné, H.E. de Melker, G.P.J.M. van den Dobbelsteen, D.W. Notermans, J. Kemmeren

4.3.1 Key points

- During 2010, two cases of tetanus in elderly, unvaccinated individuals occurred. Both survived.
- Based on cases occurring in 2011, there are indications that guidelines on post-exposure prophylaxis are not well implemented in clinical care.

4.3.2 Changes in vaccine 2010-2011-2012

See paragraph 4.1.2.

4.3.3 Epidemiology

During 2010, two cases of tetanus were reported. One of these was a man aged 71 who worked with sheep. He was admitted to intensive care for a considerable period and was discharged to a rehabilitation clinic afterwards. The second case was a 77-year-old woman who acquired tetanus when a wound on her toe was exposed to garden soil. She was admitted to hospital for over a month, and then discharged. Neither of the cases was vaccinated against tetanus since they were born prior to the start of the NIP.
Up to week 43 in 2011, five cases of tetanus have been reported in elderly (age range 66-85), of whom one was fatal. None of these cases had been vaccinated against tetanus in the past. For four of the cases, information about post-exposure prophylaxis was available. Three of these did not receive tetanus immune globulin (TIG) even though they visited a health care professional and had a clear indication for TIG.

4.3.4 Pathogen

Subtyping is not relevant for tetanus.

4.3.5 *Adverse events*

Two studies showed that diphtheria-tetanus-toxoid vaccine is well tolerated in adults who more than ten years before[41] or never[15] received a diphtheria-tetanus-pertussis (DTP) vaccination.

4.3.6 *Current/ongoing research*

Within the RIVM, no specific research is ongoing regarding tetanus. Research priorities include the re-assessment of the appropriateness of current post-exposure prophylaxis guidelines and their implementation. The cases in 2011 suggest TIG is not given when indicated, whilst vaccination may be given when there is no need. 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 were born before 1983 should be explored.[42]

4.3.7 *International developments*

Regarding tetanus, there are no international developments that require attention.

4.4 Poliomyelitis

H.G.A.M. van der Avoort, W.A.M. Bakker, W. Luytjes, H.E. de Melker, J.M. Kemmeren, N.A.T. van der Maas

4.4.1 *Key points*

- In 2010 and 2011 up till week 50, no cases of poliomyelitis were reported in the Netherlands.
- Europe has retained its polio-free status after rapid (within six months) and successful interruption of circulation of wild poliovirus type 1, imported early 2010 from India into Tadjikistan with subsequent spread to at least three other countries (Uzbekistan, Kazakhstan and Russia). No new cases have been reported in the WHO EURO Region since September 2010.
- Since the beginning of 2010 in two of the four traditional endemic countries, namely India and Nigeria, a radical decrease in the number of poliomyelitis cases of more than 97% was observed. In fact, the last case in India dates from January 2011 and India has been free of polio for at least nine months, including the traditional high circulation period during the rainy season. In two other endemic countries (Afghanistan and Pakistan), the number of polio cases has increased mainly because of serotype 1.
- In August 2011, an outbreak of wild type 1 poliovirus started in China after introduction of a polio 1 virus from a neighbouring country in Pakistan. Rapid containment of this outbreak is necessary to re-establish the polio free status of the Western Pacific Region of WHO.
- A phase I clinical trial assessing the safety and immunogenicity of an RIVM IPV-vaccine, containing attenuated Sabin strains, in adults in Poland is ongoing. The developed technology will be transferred to local vaccine manufacturers in low and middle-income countries.

4.4.2 *Changes in vaccine 2010-2011-2012*

See paragraph 4.1.2.

4.4.3 Epidemiology

Polio eradication initiative: global situation in 2011.
In the first quarter of 2011, the number of Wild Poliomyelitis Virus (WPV) cases in India and Nigeria has decreased enormously (Figure 6). Crucial for this success has been the use of bOPV, to stop circulation of wild type 1 and type 3 circulation at the same time. In order to stop type 2 VDPV circulation and to prevent creation of a subpopulation with no or low polio 2 antibodies, bOPV vaccination rounds have been complemented with at least 1 tOPV round per year. The last case of WPV caused poliomyelitis in India was reported in January 2011. India has been free of polio for more than 9 months including the traditional high circulation period during the rainy season. Only incidental cases of poliomyelitis were reported in Nigeria in 2011: sustaining and improving this status remains an enormous challenge.
In contrast: little progress was made in 2011 in Afghanistan and Pakistan, with increased circulation of WPV type 1. There was only one WPV type 3 isolation in the total Asian continent in 2011. Persisting political unrest in both countries and floods covering a large part of Pakistan have had a negative influence on the quality of vaccination and surveillance activities.
Furthermore, in 2010, nine outbreaks in polio-free countries that had started in previous years were stopped. Two new outbreaks in 2010 (Polio 1 in Congo, Chad and Uganda) and four in 2011 (Polio 3 in Côte d'Ivoire, Gabon, Mali and Niger) were detected. Molecular characterisation of the isolates from Congo and Uganda showed that these viruses are 'orphan' viruses, with relative low genetic relationship to viruses from several years ago, indicating missed circulation in the intermediate years due to inadequate surveillance. The outbreak in Côte d'Ivoire with subsequent spread to neighbouring countries started during the high political unrests after the elections in 2011. Interventions are on track to stop these outbreaks within six months after detection.
Europe has retained his polio-free status after the effective interruption within six months of an epidemic in Tadjikistan caused by importation of wild poliovirus type 1 in 2010 from India, with subsequent spread to at least three other countries (Uzbekistan, Kazakhstan and Russia). No new cases have been reported in the WHO EURO Region since September 2010.
Furthermore, in August 2011 the Ministry of Health of China confirmed the isolation of WPV1 in children and young adults, with at least ten cases (data per 12th October 2011). The viruses are genetically related to viruses currently circulating in Pakistan. Vaccination campaigns including children and young adults are held to interrupt transmission within six months and by that to retain the polio free status of the Western Pacific Region of WHO.

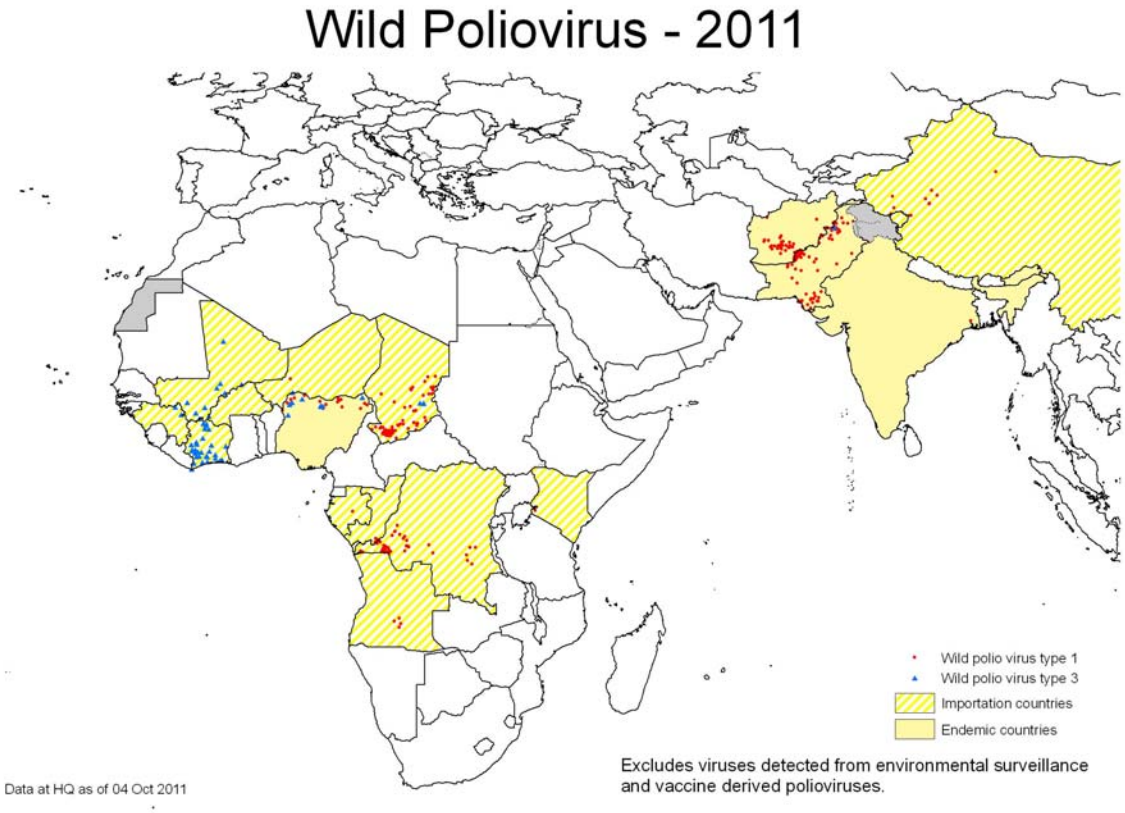

Figure 6 Wild poliovirus cases worldwide

4.4.4 Pathogen

One vaccine type 3 poliovirus (two mutations compared to the OPV 3 seed virus) was isolated from a stool specimen from a 5 month old boy from Afghanistan with meningitis and severe urosepsis that had been vaccinated two months before with OPV in his home country.
In 2011 two polio vaccine strains were reported: a polio 3 vaccine strain by screening of a historic stool collection from Bangladesh, and a polio 1 vaccine strain from an ECHO1 preparation obtained from a renowned strain library.[43] Both findings illustrate potential risks for unvaccinated populations once polio is eradicated and strict containment of wild poliovirus and OPV strains is essential.

Vaccine-derived polioviruses (VDPVs) can originate in two ways: by continued circulation of OPV viruses in unprotected populations or by prolonged excretion by immune-deficient persons. For poliovirus type 1 and 3, suspected VDPVs have ten or more nucleotide changes in the VP1 gene compared with the corresponding Sabin strains, for poliovirus type 2 the number of differences must be six at least.
These viruses can cause outbreaks of poliomyelitis, indistinguishable from wild-type epidemics. Suspected VDPVs are classified as i-VDPVs, when linked to an immune-deficient person; as circulating or c-VDPVs, when associated with two or more cases of acute flaccid paralysis; and as ambiguous or a-VDPVs in all other cases (for instance when isolated form sewage).

Table 8 Circulating vaccine-derived Poliovirus, 2000-2011 (WHO, data in WHO/HQ as of 13 Sept 2011)

Country	**c-VDPV type 1**												**Most recent case**
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	
Mozambique												2	02 June '11
Myanmar							1	4					06 Dec '07
Indonesia						46							26 Oct '05
China					2								11 Nov '04
Philippines		3											26 Jul '01
DOR/Haiti	12	9											12 Jul '01
Country	**c-VDPV type 2**												**Most recent case**
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	
Nigeria						3	22	71	66	154	27	12	28 Jun '11
Yemen												4	09 Jun '11
Somalia									1	6	1	5	24 Mar '11
Afghanistan											5	1	20 Jan '11
Chad											1		10 Nov '10
DR Congo									13	5	18		13 Oct '10
Niger							2			2	1		01 Jun '10
India										15	2		18 Jan '10
Ethiopia									3	1			16 Feb '09
Madagascar		1	4			3							13 Jul '05
country	**c-VDPV type 3**												**Most recent case**
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	
Ethiopia										1	6		04 Nov '10
Cambodia						1	1						15 Jan '06

4.4.5 Adverse events

See paragraph 4.2.5.

4.4.6 Current/ongoing research

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

4.4.7 International developments

4.4.7.1 Sabin-IPV development, clinical studies, and technology transfer

As a result of continuous WHO-efforts, polio eradication is moving forward. The first milestone, cessation of wild-type poliovirus transmission, is now anticipated by the end of 2013 (http://www.polioeradication.org/content/publications/GPEI.StrategicPlan.2010-2012.ENG.May.2010.pdf).

However, even after polio eradication, countries may consider to continue immunisation against poliomyelitis to prevent the risk of a global outbreak due to accidental or deliberate re-introduction of the virus. Following the demonstration of a proof of principle in the 1990s[44] and responding to WHO's call for new polio vaccines[45, 46], the Netherlands Vaccine Institute (NVI) continued the development of a Sabin-IPV (Inactivated Poliovirus Vaccine, based on attenuated 'Sabin' polio virus strains).

Development of Sabin-IPV plays an important role in the WHO polio eradication strategy as bio-containment will be critical in the post-OPV cessation period. The

use of attenuated Sabin strains instead of wild-type Salk polio strains will provide additional safety during vaccine production. Initially, the Sabin-IPV production process was based on a scale-down model of the current, and well-established, Salk-IPV process. In parallel to clinical trial material production, process development, optimisation and formulation research is being carried out to further optimise the process and reduce cost per dose.[47, 48] Recently, Master- and Working virus seed lots (for technology transfer purposes), and clinical trial material (for phase I studies) have been produced under cGMP conditions at industrial scale. Currently, a phase I clinical trial assessing the safety and immunogenicity in adults in Poland is ongoing.[49] Safety and immunogenicity results are expected in November 2011. Upon positive results, the study will be continued in infants.
The developed technology is planned to be transferred to local vaccine manufacturers in low and middle–income countries. The transfer of technology at the individual manufacturer site is expected to start soon. Future partners will receive the existing Sabin-IPV production process and related QC testing and are encouraged to participate in further optimization of the actual process in order to make the vaccine more affordable.

4.5 *Haemophilus influenzae* serotype b (Hib) disease

T.M. van 't Klooster, S.C. de Greeff, H.E. de Melker, G.P.J.M. van den Dobbelsteen, G.A.M. Berbers, L.M. Schouls

4.5.1 Key points

- There have been no significant changes in the number of invasive disease cases caused by *Haemophilus influenzae* serotype b (Hib) in 2010 in the Netherlands.
- Lower antibody titers in population-based sera (2006/2007 versus 1995/1996) were found in recently vaccinated infants 6-11 months of age. However, after the booster dose of 11 months of age no differences were found between the two study periods.

4.5.2 Changes in vaccine 2010-2011-2012

See paragraph 4.1.2.

4.5.3 Epidemiology

4.5.3.1 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 7, Figure 8). 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 7). In 2010 the number of cases amounted to 38. The reason for the upsurge in cases of invasive Hib disease in 2002-2005 has remained enigmatic.

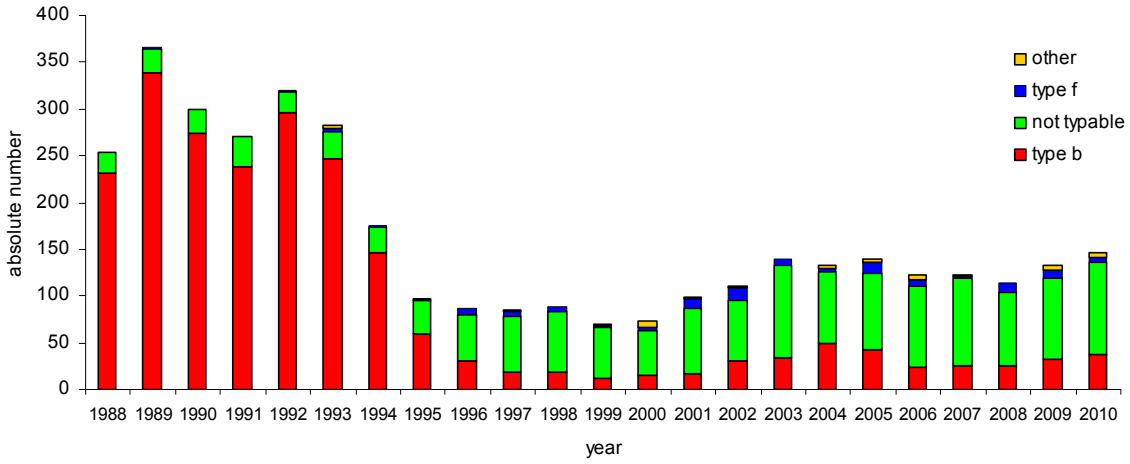

Figure 7 Absolute number of H. influenzae *isolates by serotype, 1988-2010*

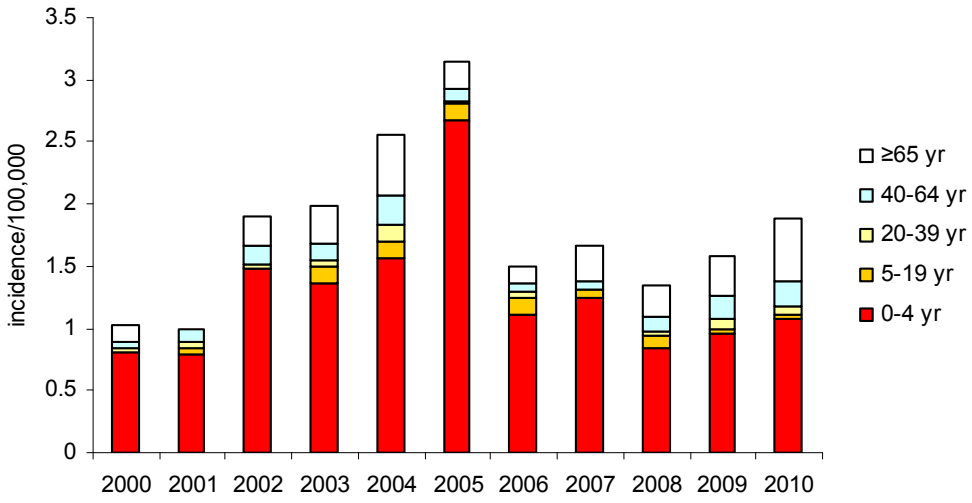

Figure 8 Age-specific incidences of patients with invasive Hib disease by year

4.5.3.2 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 9: the annual incidence per 100,000 is shown in Figure 8).

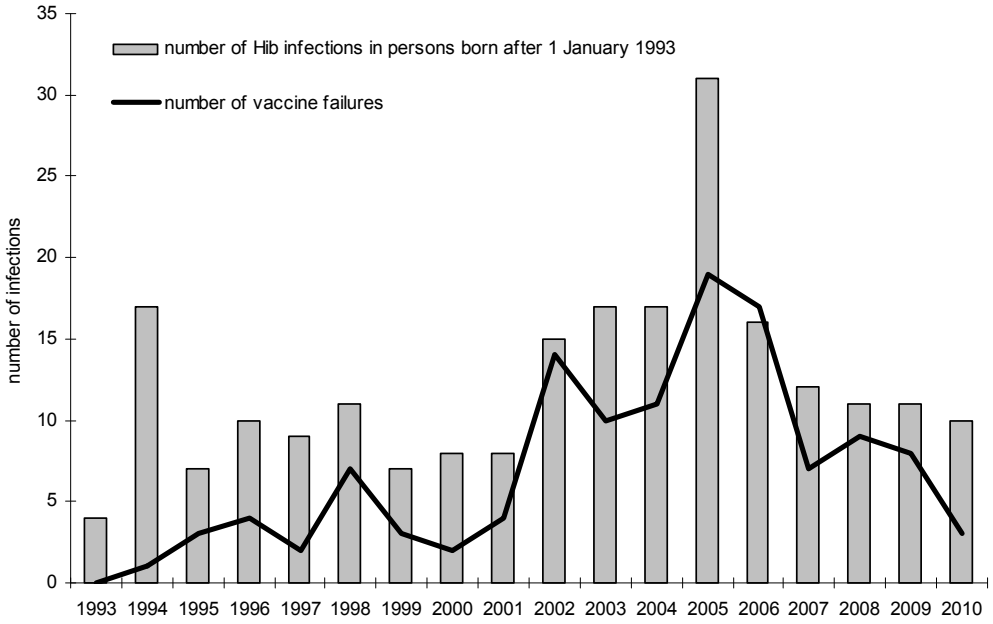

Figure 9 Annual number of Hib infections in persons eligible for vaccination (i.e., born after 1 April 1993) and the number of vaccine failures

4.5.3.3 Immune surveillance

The concentration of antibodies to the capsular polysaccharide of Hib in the Dutch population were assessed in a population-based set of serum samples collected in 2006-2007 (PIENTER 2, 7888 sera) and compared with those obtained from a similar set of serum samples collected in 1995-1996 (PIENTER 1, 9378 sera). Children 6-11 months in age (post-primary vaccination) from the PIENTER 2 study had approximately threefold lower anti-Hib antibody concentrations in their serum/blood than children from the same age group in the PIENTER 1 study. No such difference between the antibody concentrations in samples from children older than 11 months in age (post-booster) was found. Furthermore, no reduced IgG concentrations were found in age groups of 2 years and older. Although reduced immune responses were observed after the primary vaccination series, the average IgG concentration is still within the protective range and there has not been an upsurge of invasive Hib disease in the Netherlands. The reduced antibody concentration may have been caused by interference by the acellular pertussis vaccine.

4.5.4 Pathogen

There is no evidence that there have been changes in the pathogenicity of Hib.

4.5.5 Adverse events

See paragraph 4.2.5.

4.5.6 Current/ongoing research

The apparent reduced vaccine-induced immunity in children after the primary vaccination series needs to be closely monitored. One of the first opportunities to follow up on this will be the PIM-study (pneumococcal vaccination trial) where the RIVM will again test the response against Hib in 400 vaccinated children. Collection and typing of *H. influenzae* will be ongoing to monitor for possible chances in the pathogen population.

4.5.7 *International developments*

Meerveld et al. recently showed a single dose of conjugated Hib vaccine is adequate to protect of asplenic patients.[50]
GSK has developed and licensed an Hib-MenC conjugate vaccine (Menitorix). Menitorix is indicated for the prevention of invasive diseases caused by *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* group C (MenC) in infants starting from the age of 2 months and children up to the age of 2 years. This vaccine has been licensed through a mutual recognition procedure in the UK, Belgium, Greece, Ireland, Poland and Spain and has been introduced into the childhood immunisation schedule of the UK as booster vaccination for Hib and MenC vaccines at the age of 12 months.

4.6 Mumps

S.J.M. Hahné, N.Y. Rots, J. Kemmeren, R.S. van Binnendijk

4.6.1 *Key points*

- The mumps outbreak that started among students late 2009 continued in 2010 and 2011.
- The mumps outbreaks are dominated by genotype G5 mumps virus.
- The majority of cases (70%) had been fully (2*MMR) vaccinated.

4.6.2 *Changes in vaccine 2010-2011-2012*

No changes have occurred in the MMR vaccine used in the NIP during 2010.

4.6.3 *Epidemiology*

The genotype G mumps outbreak that started among students late 2009 continued into 2010 and 2011 (Figure 10). In 2010, 562 mumps cases were reported. Up to 18 October 2011, 1052 cases had been reported. Of these, 59% were male. For 86 of the 1052 cases (8.2%) a complication was recorded (Table 9), of which orchitis was the most frequent (12% men). 20 cases were admitted to hospital; none died. Vaccinated men with mumps had a lower risk of orchitis compared to unvaccinated men with mumps (see 4.6.6).
The outbreak started with clusters in Delft and Leiden. Transmission intensified during and after a student party in Leiden early 2010 (K. Greenland, manuscript submitted for publication). Student status was systematically asked for in the surveillance from mid-2010 onwards. During the outbreak, the proportion of cases not associated with students increased (Figure 11). The age distribution of cases did not markedly change during the outbreak. The majority of cases (70% of 945 cases with information) was fully (i.e. twice) vaccinated (Figure 12).

Table 9 Reported complications among the 1052 cases of mumps reported between 1st December 2009 and 18th October 2011

Complication	**% of reported cases (N=1052)**
Orchitis	12.2% of men
Encephalitis	0.0%
Meningitis	0.4%
Pancreatitis	0.2%
Thyroiditis	0.1%
Permanent deafness (one ear)	0.1%
Other	0.5%

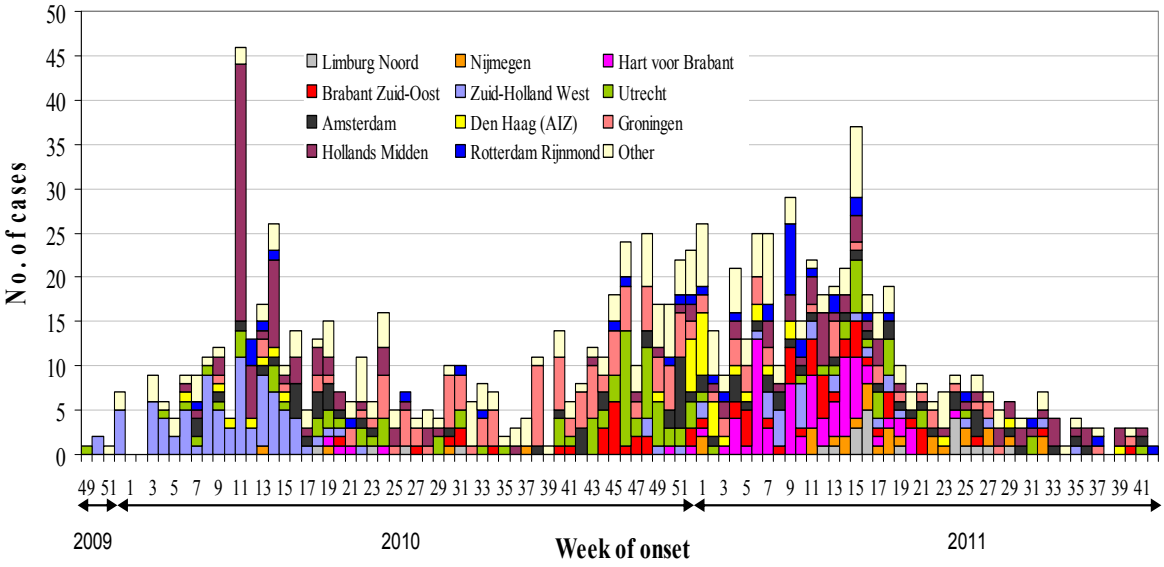

Figure 10 Number of reported mumps cases by week of onset and GGD, 1st December 2009 – 18th October 2011 (N=1052)

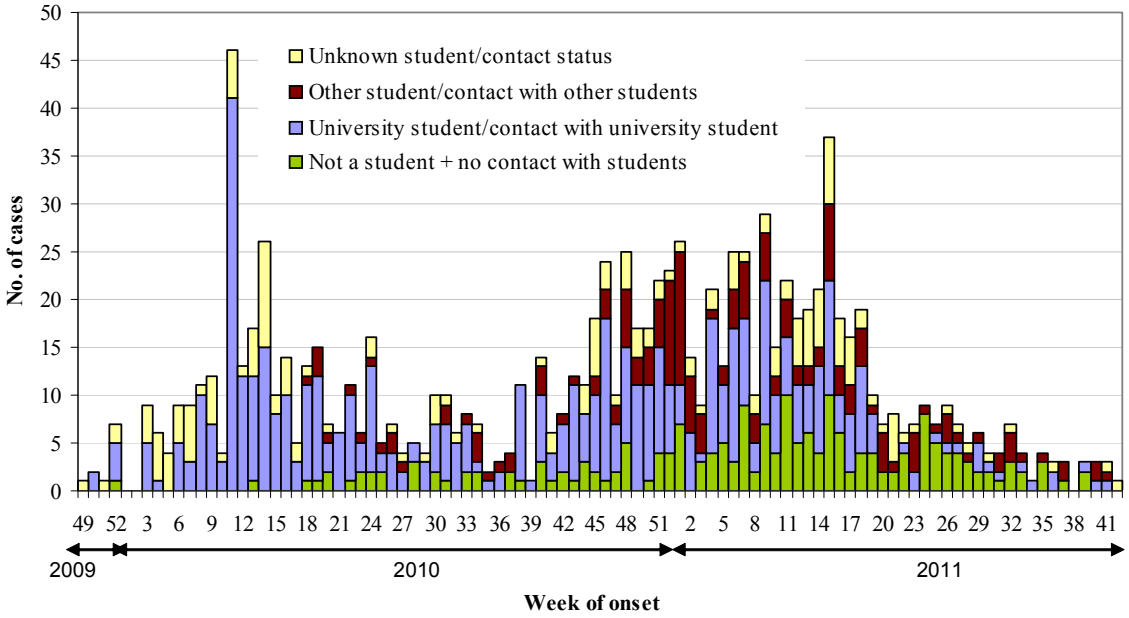

Figure 11 Number of reported mumps cases by week of onset and student status, 1st December 2009 – 18th October 2011 (N=1052)

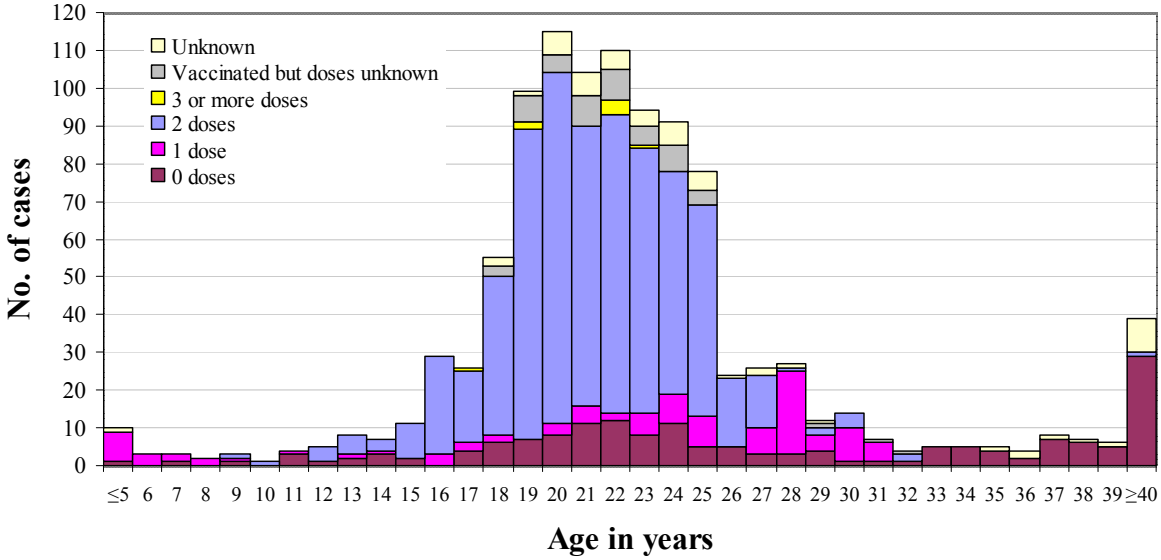

Figure 12 Number of reported mumps cases by age and vaccination status, 1st *December 2009 – 18th October 2011 (N=1052)*

4.6.4 *Pathogen*

In 2010, The RIVM laboratory investigated 1362 clinical specimens from a total of 820 suspected cases, of which 310 (38%) were laboratory confirmed on the basis of a positive virus detection by real time PCR (urine, throat swab, oral fluid). Mumps genotyping was performed by direct sequencing on most of the PCR positive specimens in 2010 (SH-gene region), which demonstrated introduction and dominance of genotype G5 throughout epidemic period, from late 2009 until July 2011.
Up to week 42, 2011, the laboratory had investigated 1133 specimens from a total of 778 suspected cases, of which 251 (32%) were laboratory confirmed.
The mumps genotype identified for the first mumps cases and outbreaks in 2010 in Utrecht, Leiden and Delft was 100% identical to the G5 mumps virus isolated from the mumps outbreaks in UK/USA between 2005 and 2009. As of April 2010, a 2-nucleotide variant of G5 has been identified in Groningen, and this variant is the primary sequence type detected in most cases reported as of august 2010. Few other genotypes (genotype D, J, H) were occasionally detected in 2010. These were cases which had no direct connection with the student population, and which did not result in secondary mumps cases. For most of these cases a travel history outside the Netherlands was identified.

4.6.5 *Adverse events*

In the Netherlands in 2010 the number of AEFI following Mumps Measles Rubella (MMR) vaccination was 263, compared with 233-315 for the time-period 2005-2009. Mostly MMR vaccination was administered simultaneously with either MenC vaccination at 14 months of age or the dT-IPV booster at 9 years of age. But since the risk periods for these vaccines are different, the AEs can be ascribed to the appropriate vaccines. The reporting rate for both MMR doses has been rather stable for the last six years.[24]

A case report of Manzotti et al. described a partial recurrent oculomotor palsy associated with systemic symptoms following MMR vaccination in a healthy 20-month-old child.[51] The oculomotor palsy did not recover completely during the

follow-up. So, although MMR vaccination has been proved to be safe and to reduce significantly the number of reported infections due to these viruses, significant AEs can occur. However, the incidence of this rare AE is unknown, but seems to be very low.
In a population-based study in the Netherlands, 32.7% of the children experienced local reactions after MMR booster vaccination at 9 years of age, and in 20.8% of the children systemic events occurred 8-21 days after vaccination.[52] Lee et al. found the same incidence in local reactions, but higher incidences in systemic events were found[53, 54], although these studies were done in children aged 4-6 years.
The assessment of rare AEs following vaccination may not be possible within a single country due to an insufficiently large denominator population. In 2008 a European consortium (VAESCO) was funded to perform collaborative vaccine safety studies. This consortium has the potential for vaccine safety collaboration across Europe to detect true associations through use of common protocols and sharing of results or data.[55]

4.6.6 Current/ongoing research

The genotype D mumps outbreak that occurred in 2007-2009 mostly in low vaccination coverage areas has been described in a recent manuscript.[56] In this, the spread of the outbreak to Canada is analysed. Specific studies concerning the viral shedding of mumps virus of vaccinated children who were in contact with mumps during the 2007-2009 epidemic and serological evidence for mumps virus transmission to vaccinated children has been published.[57, 58]
Ongoing research on assessing vaccine effectiveness and the critical vaccination coverage threshold to prevent outbreaks is pending (B. Snijders, M. van Boven, personal communication).[59] In May 2011, ZonMW funded a mumps study which incorporates three objectives (work packages) as the direct consequence of the advice of the OMT (January 31, 2011) to initiate research as to gain insight into the causative factors of the mumps outbreaks in vaccinated persons, and to better understand the burden of disease. The objectives are transmission parameters within the susceptible population and (cellular) immunity (WP1), complications of mumps-associated orchitis (WP2) and determinants of vaccine uptake among students offered catch-up vaccination (WP3). These studies are planned to start late 2011, subsequent to METC approval.
By late 2011, the results of the PIENTER 2 study into the sero-epidemiology of mumps in the Netherlands will become available (manuscript in preparation). Preliminary findings indicate that birth cohorts who have experienced mumps virus infection in the past have higher mumps specific IgG titers than those who have been vaccinated. Another finding is that waning immunity after vaccination is observed.

4.6.7 International developments

Outbreaks in vaccinated adolescents have been reported from many countries. Explanations mentioned include low vaccine efficacy due to primary and secondary vaccine failure, possibly reduced cross-protection of the wild-type mumps strain against the vaccination strain, and specific contact patterns in the affected group.

4.7 Measles

S.J.M. Hahné, J. Kemmeren, N.Y. Rots, R.S. van Binnendijk

4.7.1 Key points

- The incidence of measles in 2010 was 0.9/1,000,000 population (15 cases in total), which is just below the WHO elimination target (one per million).
- The largest cluster was of five cases, four of which were reported in December 2009.
- In the Western Europe (e.g. France), the incidence of measles increased in 2010 and 2011, reflected in an increased number of imported cases in 2011.

4.7.2 Changes in vaccine 2010-2011-2012

No changes have occurred in the MMR vaccine used in the NIP during 2010.

4.7.3 Epidemiology

In 2010, 15 measles cases were reported (0.9/1,000,000 population), just below the WHO target for elimination of 1/1,000,000. Of the 15 cases, 5 were hospitalised. No deaths occurred. The age of cases ranged between 0 and 42 years, the median age was 24. Of the 15 cases, 5 infections were acquired in the Netherlands and 10 abroad. For all cases the vaccination status was known. Of these, 13 were unvaccinated and 2 were vaccinated once. Of the 13 unvaccinated cases, 2 were too young to be eligible for vaccination, and 1 was born before introduction of vaccination. Of the 11 unvaccinated cases, it was reported for 8 whether or not they belonged to a risk group for non-vaccination. This was the case for only 2 cases (critical attitude towards vaccination). Hence, no cases were reported in unvaccinated persons based on religious or antroposophical beliefs.

1 of the 15 cases in 2010 belonged to a cluster of 5 cases (GGD region IJsselland), that mostly occurred in 2009 ('Montessori' cluster).

In 2011, up to week 43, 51 cases had been reported. This is a considerable increase compared to 2009 and 2010, and was mostly due to import from abroad, related to the measles epidemics in several west European countries including France and Italy. The majority of cases (87%) were unvaccinated for reasons including a critical attitude towards vaccination and antroposophical beliefs.

4.7.4 Pathogen

The measles virus genotype signatures was determined for 9 of the 15 reported cases; 7 were reported with genotype D4, the most widely distributed genotype in Europe, one case had been infected with genotype D9 (origin: Italy) and one with Genotype B3 (source: Kenia).

4.7.5 Adverse events

See paragraph 4.6.5.

4.7.6 Current/ongoing research

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. One component of this assesses measles IgG titers in infants born to MMR vaccinated mothers compared with infants of mothers of whom a large proportion was unvaccinated. In the former group, the duration of protection is on average 2 months shorter than in the latter group (S. Waaijenborg, personal communication). Implications of this for the MMR vaccination schedule will need to be assessed, taking into account the immunity against mumps and rubella.

At the end of 2011, the national seroprofile for measles (PIENTER 2) will become available. Preliminary results suggest that overall the Dutch population is well protected against measles. Titers are higher in birth cohorts that were infected with measles than vaccinated birth cohorts. Some indications of waning immunity following vaccination are observed. The clinical relevance of this is, however, unclear. A considerable susceptible population was found among orthodox reformed children aged 8 years or below, i.e. born after the most recent measles outbreak in 1999/2000.

Novel laboratory strategies have been developed to enhance non-invasive sampling of patients (fingerprick blood/saliva) and differential serological screening of cases and clustered outbreaks for measles. To this end, a multiplex IgM microarray has been developed at RIVM as a novel surveillance tool to provide rapid diagnosis (or exclusion) of infection and for outbreaks (measles/rubella/fifth disease, OGZ/MHS funded programme 2010/2011).

4.7.7 International developments

The incidence of measles in the WHO European Region decreased from almost 400 per 1,000,000 population in the early 1990s to around 8 per 1,000,000 in 2007-2009.[60] However, in 2010 and 2011, outbreaks of measles with over 1000 reported cases were reported from Bulgaria, France, Germany, Italy, Romania and Spain (ECDC monthly measles reporting), associated with relatively low MMR coverage in these countries. The new WHO Euro measles elimination target year is 2015. The RIVM laboratory has obtained funding from WHO-EURO in 2011 to further develop Luminex multiplex measles serology to enhance compliance (small sample volume, used of dried blood spots) and to provide standardised IgG testing for evaluation of the population immune status for VPDs (high throughput, international comparisons). To this end, the Luminex serotechnology at RIVM will be fed by nationally and internationally acquired serum banks (WHO regional labs in Berlin, Luxembourg, London) in 2011 and 2012, to assist to the WHO measles and rubella network by providing comparative data of the currently used EIA-based determinations for measles (including Luminex) and against the biologically standardised plaque-reduction neutralisation (PRN-) assay for measles, which is considered a close correlate of immune protection.

4.8 Rubella

S.J.M. Hahné, J. Kemmeren, N.Y. Rots, R.M. van Binnendijk

4.8.1 Key points

- There were no rubella cases reported in the Netherlands in 2010.

4.8.2 Changes in vaccine 2010-2011-2012

No changes have occurred in the MMR vaccine used in the NIP during 2010.

4.8.3 *Epidemiology*

During 2010 no cases of rubella were reported in the Netherlands. In 2011, up to week 43, two cases had been reported.

4.8.4 *Pathogen*

During 2010 no cases of rubella were reported in the Netherlands.

4.8.5 *Adverse events*

See paragraph 4.6.5.

4.8.6 *Current/ongoing research*

See paragraph 4.7.6 of the measles chapter. Overall, the seroprevalence is high in the Dutch population. Similar to measles and mumps, naturally infected birth cohort have higher titers than vaccinated birth cohorts.
Novel laboratory strategies have been developed to enhance non-invasive sampling of patients (fingerprick blood/saliva) and differential serological screening of cases and clustered outbreaks for rubella. To this end, a multiplex IgM microarray has been developed at RIVM as a novel surveillance tool to provide rapid diagnosis (or exclusion) of infection and for outbreaks (measles/rubella/fifth disease).

4.8.7 *International developments*

The RIVM laboratory obtained funding from WHO-EURO in 2011 to further develop Luminex multiplex rubella serology as to enhance compliance (small sample volume, used of dried blood spots) and to provide standardised IgG testing for evaluation of the population immune status for VPDs (high throughput, international comparisons). To this end, the Luminex serotechnology at RIVM will be further developed for rubella IgG antibody avidity testing. RIVM and several WHO European regional labs will supply the sera for this evaluation in 2011 and 2012 to assist to the WHO measles and rubella network by providing comparative data on the avidity of suspected cases with questionable rubella positive IgM serology (false positive rubella serology during pregnancy).

4.9 Meningococcal serogroup C disease

T.M. van 't Klooster, G.A.M. Berbers, S.C. de Greeff, P. Kaaijk, N.Y. Rots, J.M. Kemmeren, L.M. Schouls

4.9.1 *Key points*

- In 2009 and 2010, the first cases of meningococcal group C disease in previously vaccinated persons had been reported since the introduction of MenC vaccination in the Dutch NIP. However, both persons had an immune disorder which may explain the impaired immune response to the vaccine.

4.9.2 *Changes in vaccine 2010-2011-2012*

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

4.9.3 Epidemiology

4.9.3.1 Disease

Since the introduction of the conjugated MenC vaccine, the incidence of serogroup C disease has strongly decreased (Figure 13). In 2010, only six cases of invasive meningococcal group C disease were reported. Two were children aged 4 and 6 months, two were 19-year-old and the other two cases were adults (Table 10). With the exception of one person all six cases in 2010 were in non-vaccinated patients.

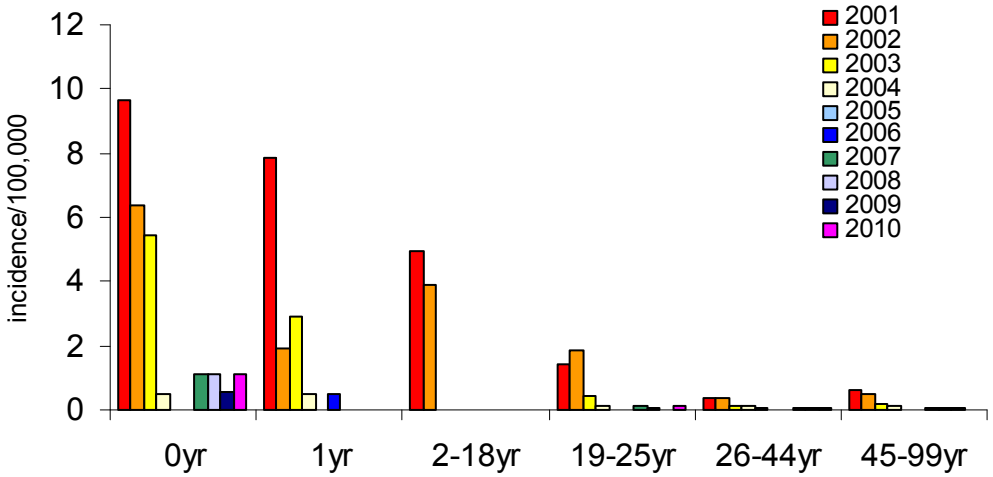

Figure 13 Age-specific incidence of meningococcal C disease by year, 2001-2010

Table 10 Absolute number of patients with meningococcal C disease

Age (Yrs)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
0	20	13	11	1	0	0	2	2	1	2
1	16	4	6	1	0	1	0	0	0	0
2-18	164	131	1	1	0	0	1	0	1	0
19-25	19	25	6	2	0	0	2	1	0	2
26-44	18	17	7	5	2	1	1	2	2	2
44-99	39	31	11	7	2	2	3	6	5	0
Total	**276**	**221**	**42**	**17**	**4**	**4**	**9**	**11**	**9**	**6**

4.9.3.2 Immune surveillance

The analysis of the nearly 8000 serum samples collected during the PIENTER 2 study revealed a gradual increase with age of vaccination in the persistence of MenC specific antibody levels in the immunised cohorts of the mass campaign even five years after the single vaccination.[61] In order to find explanations for this long term persistence, the nature and the quality of this humoral immune response was examined (avidity, subclass distribution). The age-related persistence of IgG after immunisation with the MenCC vaccine seemed to result from an increase of IgG2 levels with age, while IgG1 levels remained stable throughout the different age cohorts. It is noteworthy that the increase in IgG2 correlated with a reduced IgG-avidity with age. The response elicited by the MenCC vaccine seemed to be more a mixture of both T cell dependent and T cell independent responses in terms of humoral immunological characteristics.[62]
It is also important to monitor how this immune response develops further in the future.

4.9.3.3 Vaccine effectiveness

In 2009 and 2010, the first cases of meningococcal group C disease in previously vaccinated persons have been reported since the introduction of MenC vaccination in the Dutch NIP. It concerned respectively a 16-year-old and a 19-year-old female with both an immune disorder, which might explain the diminished immune response to the MenC vaccine.

4.9.4 Pathogen

No significant changes in the properties of the MenC strains isolated from patients with invasive disease in the Netherlands have been observed.

4.9.5 Adverse events

Several trials showed a good tolerability profile of MenACWY-CRM and MenACWY-TT in adults and adolescents, even when co-administrated with other vaccines like Tdap and HPV vaccine.[63-66] MenACWY-TT was also well tolerated in children aged < 10 years.[67]

The HibMenC-TT conjugate vaccine showed to have a good safety profile in both preterm and full-term children.[68, 69] Furthermore, the co-administration of HibMenC-TT with PCV7 and MMR showed no adverse consequences for safety when these vaccines were given concomitantly at 12 months of age or separately at 12 and 13 months of age; rather, any differences between schedules showed benefit from the concomitant administration of all three vaccines, such as lower overall proportions with post-vaccination fever.[70] In a study to the safety of PCV7 and meningococcal C conjugate vaccine administered concomitantly and individually, Wysocki et al. found that local reactions were mostly similar among the treatment groups.[71] However, the MenCC vaccine group had lower rates of some systemic events than the PCV7 + MenCC vaccine group.

4.9.6 Current/ongoing research

In infants vaccinated at 14 months of age PS-specific IgG levels as well as functional bactericidal antibody levels were decreased within a couple of years and therefore a single-dose schedule may not provide sufficient protection on the long-term. In the future the implementation of a booster vaccination might be considered and recently a study has been started (TIM study, Tweede Immunisatie MenC) to define the best timing of that vaccination early in adolescence.

4.9.7 International developments

In the UK, the current MenC vaccination schedule of three immunisations at the age of 3 months, 4 months and 12-13 months of age is re-evaluated. An alternative vaccination scheme with immunisations at the age of 3 months, 12-13 months and 13-18 years has been proposed with the intention to protect the adolescent age group.

In asplenic patients, the quantity and quality of antibodies produced after one dose of conjugated MenC vaccination is lower than that observed in healthy adults.[72]

Apart from plain MenC conjugate vaccines, also multivalent conjugate meningococcal vaccines containing the MenC component, have been developed. Currently, three tetravalent meningococcal conjugate vaccines (MenA, C, W-135, Y) have been developed for United States and European markets. In Europe, Menveo (Novartis) is indicated to protect adults and adolescents aged 11 years and above against invasive meningococcal disease caused by the four

serogroups. Menactra (Sanofi), is approved in US for use in individuals 9 months through 55 years of age. Menactra is not licensed in the Netherlands. GlaxoSmithKline (GSK) has submitted an application for a similar product in Europe. Licensure of these vaccines is based on non-inferiority clinical trials comparing fourfold rises in SBA titers after immunisation with either the conjugate or the polysaccharide vaccine. In addition, GSK has developed and licensed an Hib-MenC conjugate vaccine (Menitorix). Menitorix, is indicated for the prevention of invasive diseases caused by *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* group C (MenC) in infants starting from the age of 2 months and children up to the age of 2 years. This vaccine has been licensed through a mutual recognition procedure in the UK, Belgium, Greece, Ireland, Poland and Spain, but not in the Netherlands.

4.10 Hepatitis B

S.J.M. Hahné, F.D.H. Koedijk, J.M. Kemmeren, N.Y. Rots, H.J. Boot

4.10.1 Key points

- In 2010, 191 cases of acute hepatitis B were reported in the Netherlands (incidence: 1.2/100,000 population), a decrease of 8% compared to 2009.
- Most of this decrease is due to a decreasing number of acute HBV cases reported in men who have sex with men (MSM). This suggests that the targeted vaccination programme is effective in reducing the incidence in this group.
- In both men and women, sexual contact remains the most frequently reported risk factor for acute hepatitis B.
- From birth cohort August 2011 onwards, universal infant HBV vaccination was introduced in the Netherlands. HBV vaccine coverages for infants in the targeted NIP programme were increasing in the past year. A main concern remains the completeness of the registration of infants born to HBsAg+ mothers in Præventis.

4.10.2 Changes in vaccine 2010-2011-2012

In 2011, infants born before 1st August received Pediacel (SPM-SD). Infants at risk for Hepatitis B received Infanrix Hexa (GSK). In accordance with the recommendation of the Health Council regarding universal vaccination against Hepatitis B[12], children born from 1st August onwards receive Infanrix Hexa (GSK).

4.10.3 Epidemiology

In 2010, 191 cases of acute HBV infection were reported in the Netherlands. Compared to 2009, this is a decrease of 8% (2009: 208 cases). The incidence of acute hepatitis B notifications in 2010 was 1.2 per 100,000 population (2009: 1.3/100,000); 1.8 among men and 0.5 among women (Figure 14).

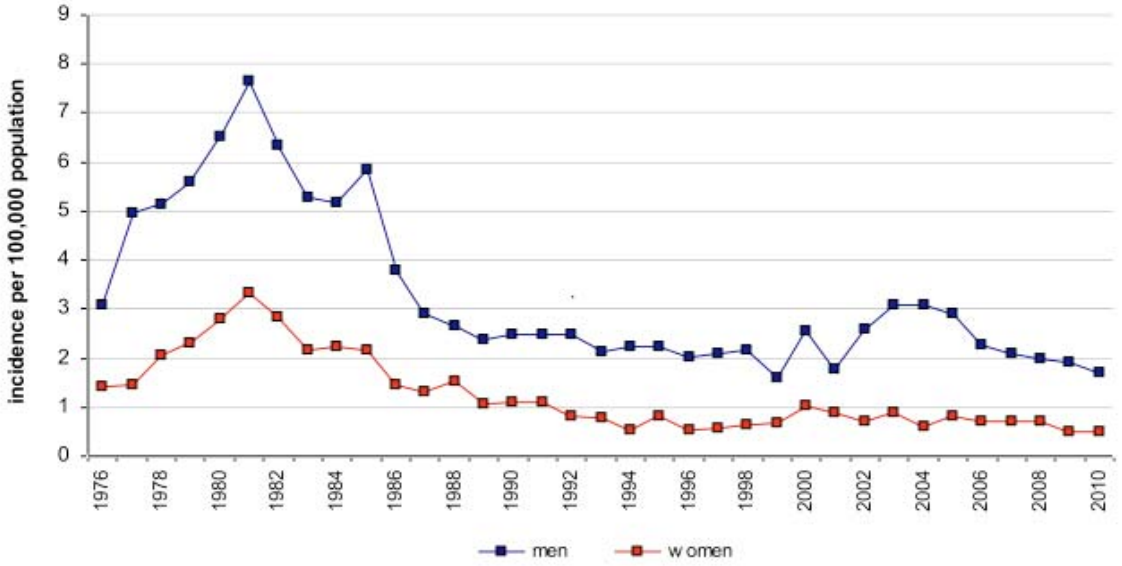

Figure 14 Incidence of notifications of acute HBV infection per 100,000 population, by gender, the Netherlands, 1976-2010 (Source: Osiris)

In 2010, sexual contact was the most reported route of transmission (65% of the 191 cases reported; for 25% of cases no risk factor was reported). Among men, 32% were MSM and 31% was due to heterosexual transmission. Among women, 65% was due to heterosexual transmission. For 25% of the reported cases of acute HBV infection the most likely route of transmission remained unknown. Most of the decrease in the number of reported cases of HBV is due to a sustained decrease in the number of cases reported in MSM (Figure 15). This suggests that the targeted vaccination programme is effective. Further details about the number of vaccines delivered in this programme can be found in RIVM's annual STI report.[73]

The effectiveness of the NIP, which up to August 2011 only included HBV vaccination for infants born to HBsAg positive mothers, children with Down's syndrome and for infants of migrants, can be assessed by the vaccine coverage in these groups. Appendix 1 and Figure 16 include these data. The HBV vaccine coverage is increasing by birth cohort.

The main concern is that not all children with the indication are correctly registered as such in Præventis. Since universal HBV vaccination is now started, this is mainly a concern for the birth dose of vaccine and HBIG for infants born to positive mothers (with D-indication). In 2010, there were 538 infants with a D-indication and 184,397 live births (0.29%) whilst the latest antenatal prevalence estimate (2008) was 0.33%.[74] This suggests not all infants born to HBsAg positive mothers are registered as such. A number of these will have been absent from registration due to peri- or neo-natal death and migration. It is therefore not straightforward to assess the completeness of registration.

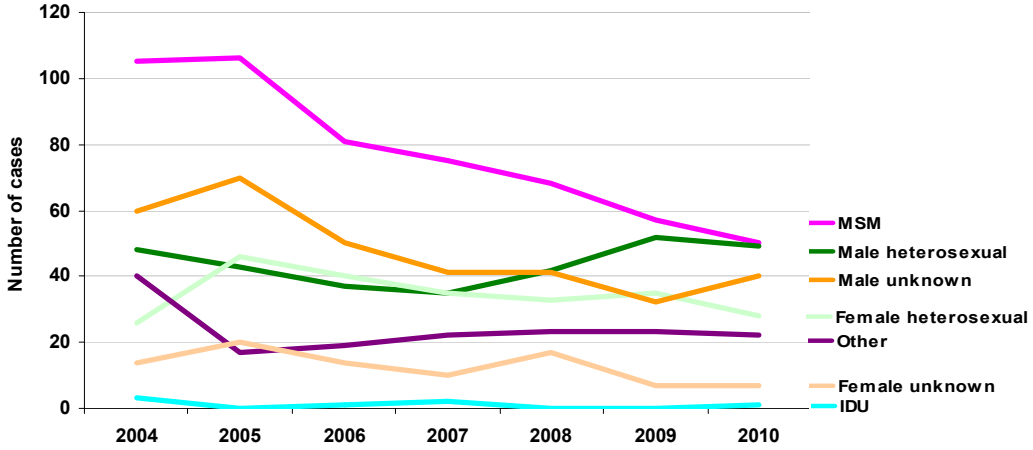

Figure 15 Number of cases of acute HBV infection by reported route of transmission and year, the Netherlands, 2004-2010 (n=1687)

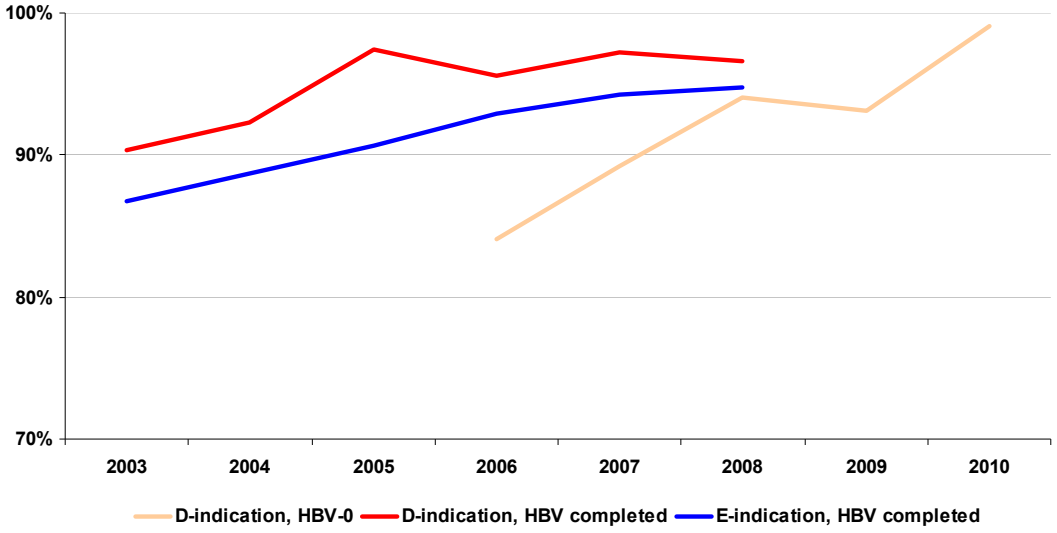

Figure 16 Vaccine coverage for infants targeted for HBV vaccination in the NIP, birth cohorts 2003-2010.[11]

D-indication: Mother is HBsAg positive. E-indication: one or both parents are born in a country with medium or high HBV prevalence.

D-indication, HBV-0 coverage here displayed is the coverage at the age of 3 days.

The coverage for infants with Down's syndrome within the NIP started in 2008. The coverage for this birth cohort was 94.3%.

The numbers accompanying this table can be found in Appendix 1.

4.10.4 Pathogen

For 103 reported cases in 2010 (54%), an S-region sequence was available. The minimum spanning tree cluster analysis showed that the subtype A2 strain that circulated predominantly among MSM, remains the most frequent strain found. No other large clusters have been observed (Figure 17).

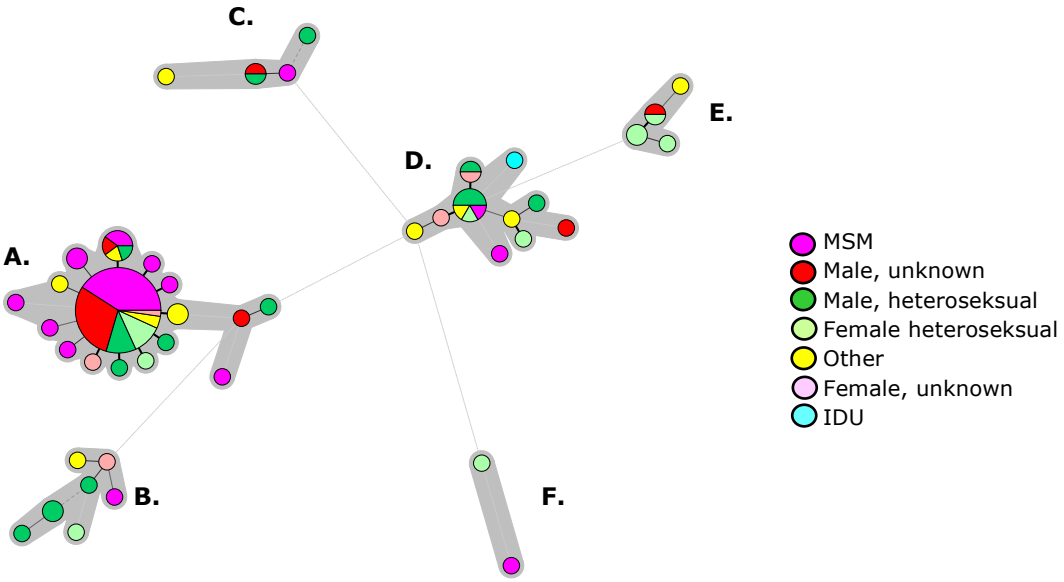

Figure 17 Minimum spanning tree of acute HBV strains in the Netherlands, by reported route of transmission, 2010 (n=103). Genotypes are indicated by the letters A-F

4.10.5 Adverse events

Dhillon concluded in a review that the reactogenicity and safety of Infanrix hexa as primary and booster vaccination was safe in infants aged < 2 years, regardless of vaccination schedules.[75] Most solicited local and general symptoms with Infanrix hexa were mild to moderate in intensity and the vaccine was associated with few unsolicited AEs. This was confirmed by Lim et al. in a study about safety and reactogenicity of DTaP-HBV-IPV/Hib and DTaP-IPV/I-Hib vaccines in a post-marketing surveillance setting.[76]

Several phase II and phase III studies assessed the safety of a new fully liquid, hexavalent investigational DTaP-IPV-HepB vaccine (Hexaxim), which incorporates a new, Hansenula polymorpha-derived, thimerosal-free hepatitis B component. This vaccine showed to be safe with control vaccines[77-79], even when co-administrated with PCV7.[80] Furthermore, no safety issues were found in studies to the safety of hexavalent primed children boosted with monovalent hepatitis B vaccine[81], the reactogenicity of DTaP-IPV/Hib vaccine co-administrated with hepatitis B vaccine for primary and booster vaccination[82], the safety of a Hib-Hepatitis B vaccine administered with concomitant pneumococcal vaccine to infants[83] and the safety of a modified process hepatitis B vaccine.[84]

Four studies assessed the safety of a DTwP-HBV/Hib combination vaccine. All studies concluded that this vaccine was well tolerated by infants[85-87], even in an accelerated vaccination schedule at 6, 10 and 14 weeks of age.[88] Two studies evaluated co-administration of HPV-16/18 AS04-adjuvanted vaccine (HPV) and hepatitis B vaccine. Both studies concluded that co-administration was generally well tolerated in adolescent girls aged 9-15 years[89] and in healthy women aged 20-25 years.[90] Administration of an accelerated hepatitis B vaccine in high-risk pregnant women was also well tolerated.[91]

The Cochrane Collaboration tried to assess the benefits and harms of booster dose hepatitis B vaccination for preventing hepatitis B infection in a review. However, there were no eligible randomised clinical trials fulfilling the inclusion criteria of the review.[92]

4.10.6 Current/ongoing research

Current HBV related research focuses on further evaluating the targeted vaccination programme for behavioural high-risk groups, transmission dynamics especially in MSM. Regarding the evaluation of the programme, coalescence methods to study changes in genetic diversity over time were explored by van Ballegooijen et al. in 2009[93] studying HBV transmission in Amsterdam. These methods are currently being applied to national data. Further work using molecular data will study the relative contribution of chronic versus acute cases to HBV transmission.

Transmission dynamic modelling is ongoing to describe transmission of HBV among MSM, and to assess the impact of the targeted vaccination programme.

In 2011 a study was completed into the seroprotection afforded by Infanrix hexa (Whelan, submitted for publication). Target thresholds for immune responses were achieved for all antigens studied. Over 99% (163/164) of children vaccinated with Infanrix hexa achieved an adequate immune response (≥ 10 mIU/ml) to the HBV component. However, peak anti-HBs geometric mean concentration (GMC) was 2264 mIU/ml (95%CI:1850-2771 mIU/ml), twofold lower than has been reported in other studies. The GMC of a pertussis component, filamentous hemagglutinin (FHA) was lower in children vaccinated with Infanrix hexa and Prevenar than in children vaccinated with Infanrix-IPV+Hib.

4.10.7 International developments

In October 2011 an EU funded project was started aiming to assess, describe and communicate to public health professionals the tools and conditions necessary for implementing successful screening programmes for hepatitis B and C among migrants in the European Union. This project is lead by the MHS Rotterdam/EMC and includes 12 European partner institutions, including RIVM.

4.11 Pneumococcal disease

T.M. van 't Klooster, S.C. de Greeff, H.E. de Melker, G.A.M. Berbers, G.P.J.M. van den Dobbelsteen, N.Y. Rots, J.M. Kemmeren, L.M. Schouls

4.11.1 Key points

- The introduction of vaccination against pneumococcal disease in the NIP 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.

4.11.2 Changes in vaccine 2010-2011-2012

There have been no changes in the composition or vaccination schedule for pneumococci in 2010. Children born after 1st March 2011 receive a 10-valent vaccine (Synflorix, GSK) instead of the 7-valent vaccine (Prevenar, Pfizer) in the Netherlands.

4.11.3 Epidemiology

4.11.3.1 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).

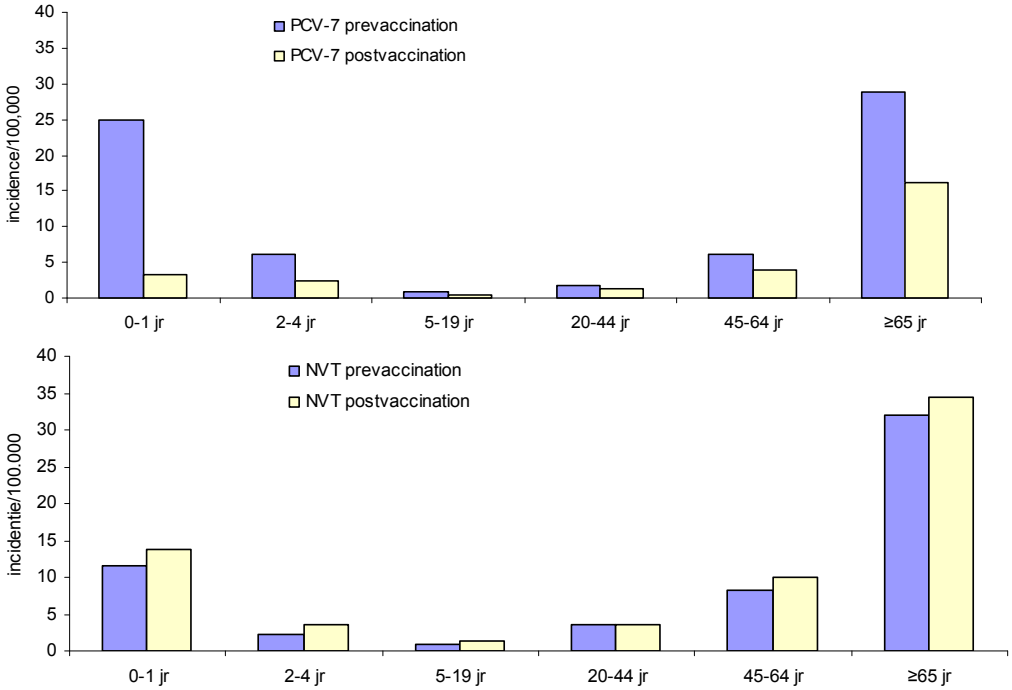

Figure 18 Age-specific incidence of vaccine type IPD (upper figure) and non-vaccine type IPD (lower figure).
In blue: before introduction of vaccination (June 2004-June 2006), and in yellow: in the post-vaccination period (June 2006-July 2011). Incidences are calculated on cases reported by the nine sentinel labs, but extrapolated for the whole population.

Vaccine-type IPD decreased by 87% in children < 2 years of age. A reduction of vaccine type IPD has also been observed in other age groups (Figure 18). However, this reduction has been partly counterbalanced by an increase in non-vaccine type IPD (Figure 18). The overall incidence in IPD in the 0-1, 2-4, and ≥ 65 yrs age groups decreased by 51%, 28% and 13%, respectively. In the 5-19 yrs, 20-44 yrs and 45-64 yrs age groups, the incidence remained stable.

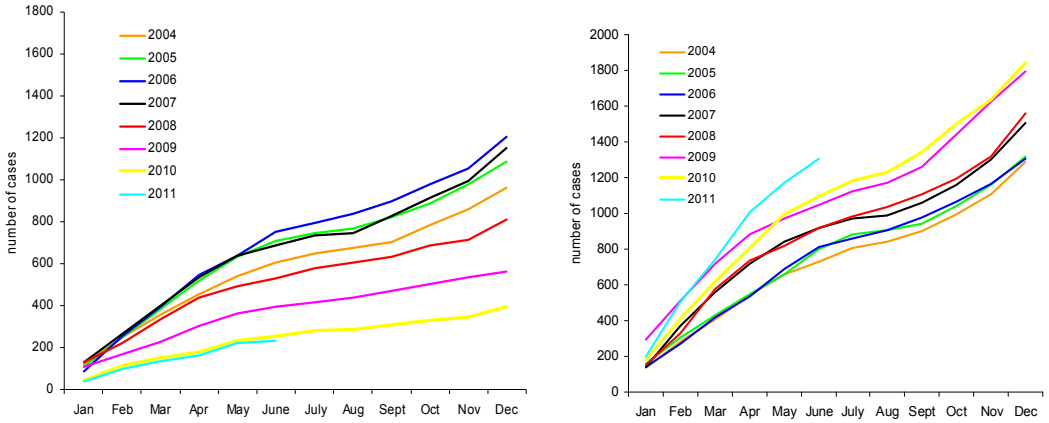

Figure 19 Cumulative number of vaccine-type IPD (left) and non-vaccine type IPD (right) per year in patients older than 2 years of age.

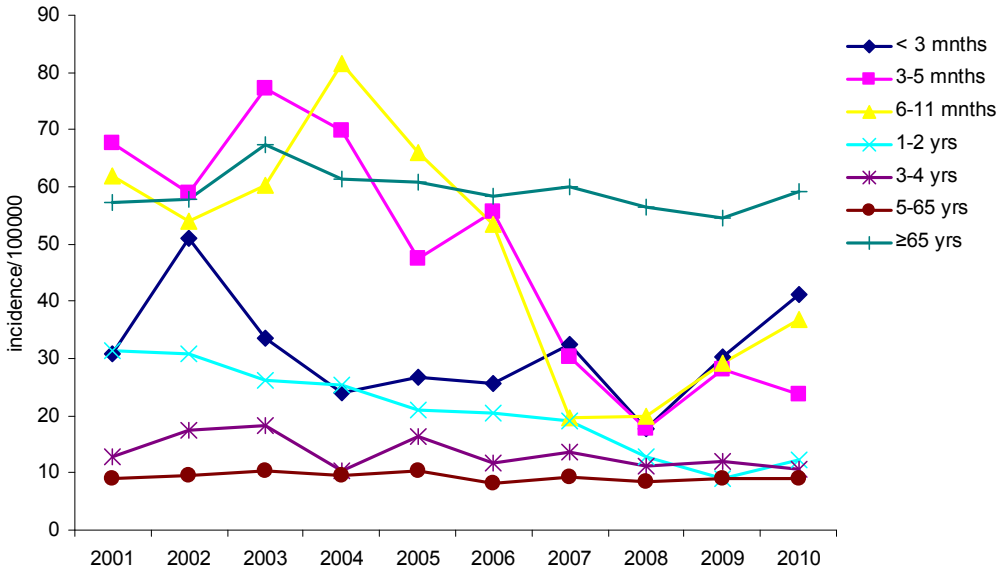

Figure 20 Age-specific incidence of hospitalisation due to pneumococcal disease (i.e. ICD9 codes 3201 (pneumococcal meningitis), 0382 (pneumococcal septicemiae), 481 (pneumococcal pneumoniae) and 4823 (pneumoniae by Streptococcus)

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*) – slightly increased in children younger than 3 months and in children 6-11 months old. This is mainly due to a little increase in the number of hospitalisations because of pneumoniae, but the numbers are very small.

4.11.3.2 Immune surveillance

The nearly 8000 serum samples collected during the PIENTER 2 study (2006/2007) were analysed in a multiplex immuno-assay that simultaneously measures in one sample 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 assessed the prevalence of antibodies induced after natural exposure to the pneumococci, because the implementation of the vaccine coincided with collection of the samples of the PIENTER 2 study. This study therefore is to be regarded as a base-line 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 developed antibodies against an increasing number of different serotypes with increasing age. Importantly, there was no uniform relationship between the occurrence of serotypes causing invasive pneumococcal disease (IPD) and the GMCs against these serotypes.[94]

4.11.3.3 Vaccine effectiveness

Up to October 2011, eight vaccinated children have been reported with vaccine type IPD (Table 11).

Table 11 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	-

4.11.4 Pathogen

No obvious changes in the properties of the pneumococci isolated from patients with IPD have been observed.

4.11.5 Adverse events

Two studies showed that immunisation with PCV7 appeared safe in preventing IPD in Thai and Japanese children, respectively.[95, 96] The same result was found for PCV10 in Chilean children.[97] The safety profiles of two vaccination schedules (three-dose primary booster or two-dose catch up) were in line with previous studies. Furthermore, Scott et al. showed that PCV7 is safe when given to newborns, which is important for developing countries were the incidence of invasive pneumococcal disease peaks at age 6-11 months.[98]

Studies conducted to compare the safety of PCV10 with PCV7 showed no differences in safety and reactogenicity profiles between these vaccines[99, 100], also when co-administrated as a booster dose with DTwP-HBV/Hib and poliovirus vaccines to toddlers primed with the same vaccines. The same results were found when PCV13 were compared with PCV7.[101, 102] In preterm children both PCV7 and PCV10 are well tolerated.[103, 104]

4.11.6 Current/ongoing research

The nationwide use of the pneumococcal vaccine which is composed of capsular polysaccharides conjugated to a protein carriers may result in the selection of

variants that are less sensitive to the vaccine-induced immunity. Therefore, we have studied the variation of genes coding for the capsule and found considerable variation within the serotypes.[105] Currently these variants are being tested to assess the consequences of these genetic changes for their sensitivity to vaccine-elicited antibodies.
Several clinical trials are being or will be performed. The vaccination and blood sampling in a pneumococcal vaccination trial, the PIM-study, with PCV7 and PCV13 is nearly finished. In this trial reduced (2+1 vs. 3+1) and differently timed vaccination schedules are compared with the currently used vaccination schedule. Results will be available in 2012. Data on PCV10 will be collected in the PIEN-study, also evaluating the cellular immunity after PCV10 or PCV13 vaccination. In addition, pneumococcal carriage in the nose and nasopharynx has been monitored before, and 3 and 4.5 years after introduction of PCV7 in the NIP to evaluate the effect of vaccination on vaccine and non-vaccine serotypes. Within 4.5 years after introduction of PCV-7, vaccine serotypes are virtually eliminated in children and parents. However, non-PCV7 serotypes (e.g. 19A) are rising.
Vaccines consisting of a common protein instead of polysaccharides of *Streptococcus. pneumoniae* may provide protection against multiple serotypes. Pneumolysin (PLY) is a cholesterol-binding, pore-forming protein toxin. It is an important virulence factor of *S. pneumoniae* and a key vaccine target against pneumococcal disease. NVI/RIVM has in collaboration with Sanofi developed detoxified mutants of PLY. New mutant PLYD1 was examined *in vitro* (hemolytic activity, cytokine induction) and *in vivo* (animal challenge models) at the NVI. Furthermore, combination vaccines consisting of three pneumococcal proteins were also tested in mouse challenge models.

4.11.7 International developments

Merck has started clinical studies with a 15-valent pneumococcal conjugate vaccine. This vaccine adds serotype 22F and 33F to the serotypes covered by Prevnar 13. GSK has started a clinical study in the Gambia to increase the coverage of Synflorix by adding several pneumococcal proteins to the conjugates.
Intercell and Sanofi both have a clinical program running with a combination of several protein vaccine candidates These proteins will induce immune responses that are not serotype specific and thereby increasing the possible coverage of pneumococcal vaccines.

4.12 Human papillomavirus (HPV) infection

M. Mollers, T.M. van 't Klooster, H.J. Boot, W. Luytjes, J.M. Kemmeren, N.A.T. van der Maas, E.A. van Lier, H.J. Vriend, J.A. Bogaards, H.E. de Melker

4.12.1 Key points

- In 2011, the interim vaccination coverage for the third dose in the first NIP cohort, i.e. girls born in 1997, was 52.5%. The coverage for three doses among girls of the catch-up campaign increased to 52.3% in 2011.
- In 2010, the profile of adverse events was similar to 2009 with a somewhat lower reporting rate.
- Prior to vaccination, HPV DNA prevalence was estimated in the Netherlands in various studies to enable monitoring changes in HPV type distribution after vaccination.
- Vaccine types HPV16 and 18 are found in approximately a quarter of the HPV positive women.

4.12.2 Changes in 2010-2011-2012

Currently, the bivalent vaccine (Cervarix) is used in the Netherlands. In 2012 the HPV-vaccine product for the NIP will be tendered again.

4.12.3 Epidemiology

4.12.3.1 Immune surveillance data

In 2011, a few studies estimated the HPV DNA prevalence in the Netherlands before or shortly after the introduction of vaccination. In all studies the same HPV-DNA test was used, i.e. SPF10/LIPA which identifies 15 high-risk (hrHPV) types and 12 low-risk (lrHPV) types.[106] Amongst 14- to 16-year-old girls (n=1800) who participated in a prospective cohort study (see also 3.12.6), the HPV prevalence measured before introduction of vaccination was low (4.4% for any HPV type and 2.7% for a high-risk type (hrHPV)). In contrary to this low prevalence, two other studies amongst women participating in a Chlamydia Screening Implementation (CSI) programme[107] and amongst STI centre attendees showed a much higher prevalence. For the CSI study the HPV-prevalence among 3034 women aged 16-29 was 54% (any HPV type) and 42% (hrHPV). A study amongst STI attendees aged 16-24 showed an even higher prevalence of 72% (n=1136) for women and 54% (n=430) for men for any HPV. HrHPV was found amongst 58% of the women and in 40% of the men.[108] Vaccine types 16 and 18 were present in approximately a quarter of the infected women in all three studies mentioned. Besides these two vaccine types, type 51, 52, 53, 31, 66 and 6 are the most prevalent types found. Differences in HPV prevalence are probably due to the different study population (age, sexual behaviour). Furthermore, comparing above mentioned prevalence estimations with other studies should be done with care, because the sensitivity of the laboratory tests (PCR) varies.

Besides DNA, which is a marker for a current infection, serology can provide us with information about past exposure (although not all people with a HPV infection seroconvert).[109] To obtain insight into the age-specific seroprevalence in the Netherlands, approximately 6300 sera of 0- to 79-year-old men and women were tested for HPV16, 18, 31, 33, 45, 52, 58 antibodies. This study (PIENTER 2) was performed in 2006-07, before the introduction of the HPV vaccination. An increase in seroprevalence was observed at the start of adolescence (from 15 years onwards) and was most pronounced for HPV16 in women. For the other HPV types a more gradual increase was observed. Relatively stable seroprevalences were found in middle-aged cohorts and a slight decrease in elderly. Women were more often seropositive than males, and approximately 10% of the population older than 14 years of age was seropositive for two or more HPV types indicating infection with multiple HPV types or cross-reactivity with phylogenetically related HPV types.[110]

4.12.3.2 Vaccine effectiveness

Until now, the bivalent vaccine has been proven to be effective against persistent infection for 8.4 years[111] and the quadrivalent vaccine for at least 42 months.[112-116] Recently it was reported in a posthoc analysis that women who only got two doses (instead of three doses) of the bivalent HPV vaccine also had a high VE against incident HPV16 and HPV18 infections. The VE for two and three doses was essentially the same[117] and amounted to 84.1% (95% CI = 50.2% to 96.3%; 3 and 17 events) for two doses, and 80.9% (95% CI = 71.1% to 87.7%) for three doses.

For one dose, the VE was also high but numbers were limited. Whether fewer than three doses also provide cross protection and a prolonged antibody response has to be explored. Furthermore, the bivalent vaccine has been proven

to be effective and safe in older women. The bivalent vaccine induced high and sustained immune responses in women aged 15-55 years, with antibody levels remaining several-fold higher than natural infection levels for at least four years after the first vaccine dose. [118]

4.12.3.3 HPV related cancers

Apart from cervical cancer, HPV is also related to vaginal, vulvar, penis, anus, mouth and oropharynx cancer. The number of cases and deaths due to these cancers are presented in Table 12 and Table 13. 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[119], 40-64% of oropharyngeal cancers[120, 121], and at least 3% of oral cancers.[122]

Table 12 Number of new cervical, ano-genital, mouth and pharynx cancer cases in the Netherlands from 2000-2009, by cancer type (The Netherlands Cancer Registry (NKR))

Cancer type		'00	'01	'02	'03	'04	'05	'06	'07	'08	'09
Cervix (C53)		687	604	651	606	706	683	687	737	704	707
	- Vulva/vagina (C51-52)	278	291	292	317	307	322	342	377	364	408
Ano-genital	- Penis (C60)	77	93	103	104	117	110	118	113	131	142
	- Anus (C21)	113	126	110	135	110	131	153	141	161	159
Mouth (C01-06)		795	780	782	853	876	904	874	893	924	978
Pharynx (C09-14)		505	515	525	527	561	534	563	554	639	647

Table 13 Number of deaths related to cervical, ano-genital, mouth, oropharynx and pharynx cancer cases in the Netherlands from 2000-2010, by cancer type (CBS)

Cancer type		'00	'01	'02	'03	'04	'05	'06	'07	'08	'09	'10
Cervix (C53)		258	243	187	214	203	235	214	204	244	209	205
Ano-genital	- Vulva/vagina (C51-52)	108	101	111	118	98	106	114	101	118	128	138
	- Penis (C60)	20	23	13	20	23	21	14	31	26	24	33
	- Anus (C21)	26	34	32	22	24	38	26	26	33	39	41
Mouth (C01-06)		223	216	208	254	238	234	231	239	235	268	276
Oropharynx (C09-10)		89	95	102	110	111	87	97	94	94	104	119
Pharynx (C09-14)*		245	252	284	267	289	239	275	250	266	295	270

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

As a result of changes in sexual behaviour and decrease of cervical cancer due to screening and vaccination, the relative contribution of these other HPV related diseases will increase.

In the Netherlands, a study is ongoing to assess the prevalence and the clinical relevance of HPV in a cohort of Dutch patients with Oropharyngeal squamous cell carcinoma (OroSCC). Recent studies have identified HPV as another independent risk factor for these carcinomas. There is still major controversy on vital issues of HPV prevalence in OroSCC. In total 18.5% of all OroSCCs diagnosed in two different hospitals (EMC and VUMC) from 2000 to 2006 in the Netherlands showed an oncologic HPV subtype. Compared to studies in other countries, this percentage is relatively low. The HPV subtypes identified (HPV type 16, 18, 33 and 35) are in accordance with literature reports[123] and emphasize the potential effect of vaccination on HPV related diseases other than cervical cancer.

4.12.3.4 Genital warts

In 2010, the number of diagnoses of genital warts reported in the national surveillance of STI centre remained the same (2729 in 2010 versus 2726 in 2009). At GPs, the number of reported diagnoses of genital warts was estimated at 21,654 (95% CI 17,374–27,337) in 2009 (53% men and 47% women), a small increase of 7% compared with 2008 (22,559 95% CI 17,432-29,780). In particular, the number of diagnoses of genital warts among men increased by 13% compared with 2008.[73]

4.12.4 Pathogen

HPV is a stable DNA virus that is not expected to shift (replacement of HPV16/18 by other HPV types) or drift (changes in the amino acid sequence of the HPV 16/18 L1 and L2 capsid proteins).[124] A few studies have recently confirmed the unlikeliness of these events to happen, although HPV33 should be monitored.[125] Type replacement in the Netherlands will be assessed through the HPV cohort study (see current/ongoing research) and the STI centre surveillance. These repeated measurement studies (either longitudinally or repeating cross sectional) give an opportunity to detect shifts or replacements of HPV types as a result of the vaccination campaign.

4.12.5 Adverse events

In 2010, immediate occurring AEs during mass vaccination occurred in 7.7 per 10,000 administered doses. Presyncope and syncope was most frequently reported (5.8 per 10,000 administered doses). No anaphylactic shock was reported.[126]

During 2010, the RIVM received 129 spontaneous reports of AEs following vaccination against HPV, resulting in a reporting rate of 5.4 per 10,000 administered doses. The reporting rates for girls born in 1997 (regular NIP) and for girls born in 1993-1996 (catch-up campaign) were more or less equal (Figure 21). In 23% a so-called major event was reported, of which 80% was considered to be related to the vaccination.[126]

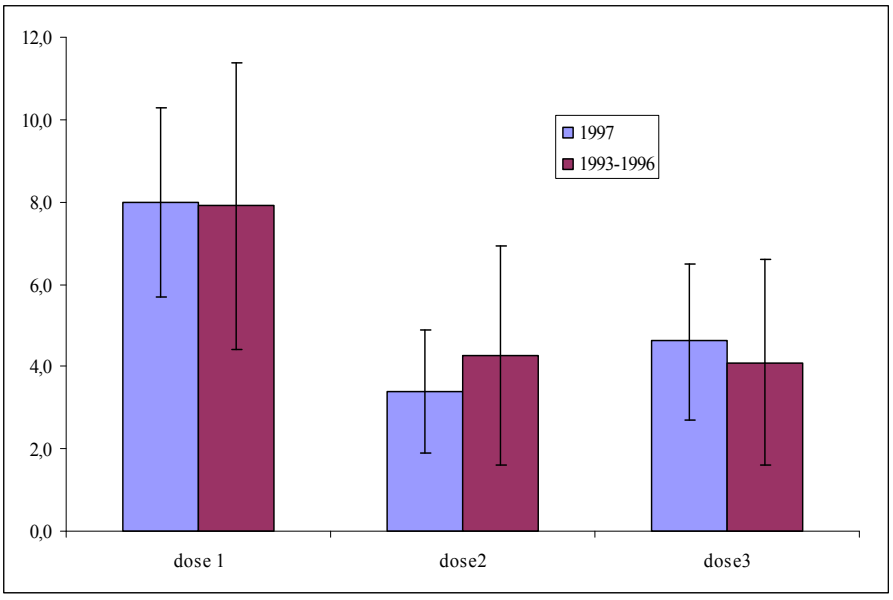

Figure 21 Dose specific reporting rates following HPV vaccination in 2010 for cohort 1997 and cohort 1993-1996

In the questionnaire study on AEs in 2010, 2308 girls (65%) participated. Local reactions occurred in 88.5%, 79.5% and 79.2% of the girls, respectively after the three doses (Figure 22). The occurrence of systemic AEs was reported in 85.9%, 74.5% and 75.8% after the three successive doses, respectively (Figure 23). In addition, for some of the local reactions and systemic AEs the incidence increased with age, and most incidences were lower after the second and third dose than after the first dose.[126] Overall in 2010, no SAEs were reported that were considered to be causally related to the vaccination.

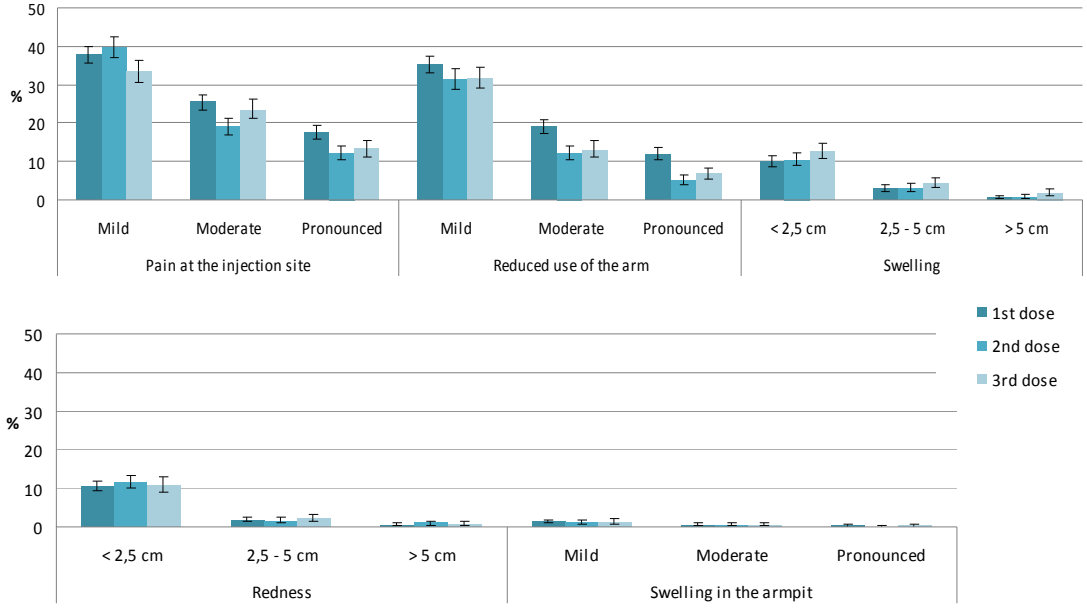

Figure 22 Incidence of local reactions by severity and dose, for cohorts 1993-1997

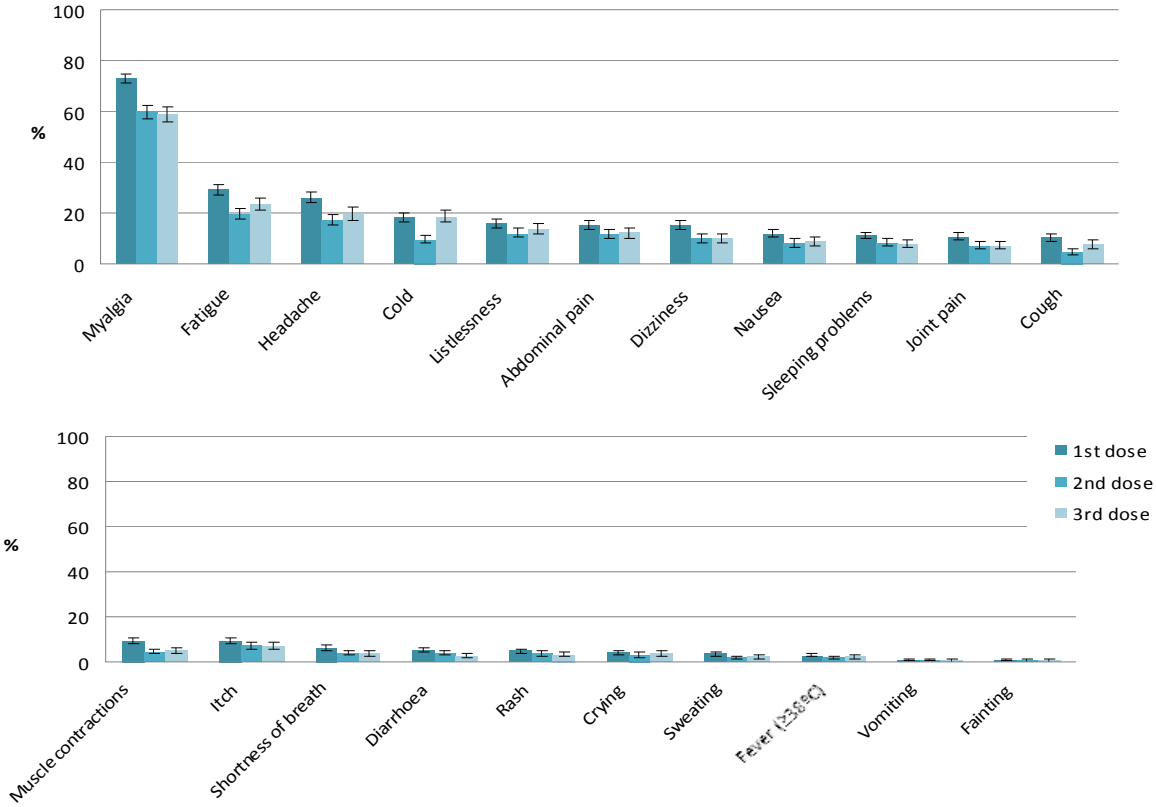

Figure 23 Incidence of systemic AEs by dose, for cohorts 1993-1997

4.12.6 Current/Ongoing research

4.12.6.1 Determinants for HPV vaccine uptake

At the start of 2011, a study was performed on HPV vaccine uptake and associated determinants. There are some clear differences among the unvaccinated girls and the dropout girls in 2009 (girls who started initially, but did not complete the series of three vaccinations) compared to the girls who were vaccinated according to the regular programme, i.e. in fewer cases the parents were born in the Netherlands; more of them lived in a big city; and a relative high percentage had a low socioeconomic status. Furthermore, relatively more unvaccinated girls live in areas with a higher proportion of voters for Religious Political Parties than girls vaccinated according to the regular programme. Late adopters in 2009 (girls who did not start with the vaccination initially, but started later on in the campaign) differed similarly concerning socioeconomic status and place of residence from the girls vaccinated according to the regular programme compared to the dropout girls in 2009. Late adopters in 2010 were comparable in background characteristics with girls vaccinated according to the regular programme. In conclusion, not (fully) getting vaccinated seems to be associated with ethnicity, socioeconomic status and religion. This should be taken into account in the communication to improve the vaccination coverage.

4.12.6.2 Linking vaccination status daughters with screening behaviour mothers

Information on the association between participation in the vaccination programme and the screening programme including potential risk groups for non-participation are essential for estimating the future impact of cervical cancer prevention (see also 3.12.6.1). That is why Steens et al. (submitted) studied the link between these two programmes in the Netherlands.[129] They found that if a

mother's screening participation is taken as proxy of a girl's future screening behaviour, only 13% of the girls will not participate in any prevention programme compared to 23% non-participation if only screening is available. The positive association between vaccination and screening participation results in slightly lower model estimates of the impact of vaccination on cervical cancer incidence compared to estimates of models assuming random participation. Girls with young mothers, with non-western ethnicities, or girls who live in urban areas with low SES are at risk for non-participation. We conclude that a part of potential non-screeners can be reached through vaccination.

4.12.6.3 HPV prevalence

A five-year prospective cohort study, which was initiated in 2009 among 15- and 16–year-old vaccinated and unvaccinated girls, is still ongoing. The primary aim is to monitor the effect of vaccination on type distribution amongst these two groups. The first baseline results which were taken prior to vaccination (see 3.12.3) show a low HPV DNA prevalence. In future years (round three is almost completed) the relationship between HPV DNA, antibodies (mucosal and systemic) and cellular immunity will be explored.

4.12.6.4 Modelling

The long-term impact of HPV vaccination in the Netherlands has been explored by mathematical modelling.[130] Underlying these projections was a type-specific transmission model[131] that had been calibrated to pre-vaccine data from a population-based study on HPV DNA testing in cervical screening. Currently, we are using data on HPV DNA prevalence in sexual health service clinics to further calibrate this model, specifically with regard to male HPV infection. The transmission model may need some adjustments to match observed data among young men and women, specifically a lower male-to-female transmissibility than vice-versa and a lower degree of natural immunity in males than previously assumed. HPV serology from sexual health service clinics and information from longitudinal studies among young women will provide opportunities to further test our HPV transmission model.

The efficiency of including boys in the HPV vaccination programme has been studied from a multi-modelling perspective, to account for uncertainty both in the natural history of HPV infection and in our type-specific HPV transmission model. From this research, we have identified several general rules when to vaccinate one sex versus the other in two-sex transmission models.[132] Key conclusion with regard to HPV vaccination are: (i) Female vaccination is more effective than male vaccination in reducing overall HPV infection levels unless male-to-female transmissibility is substantially lower than female-to-male transmissibility; (ii) Increasing vaccine uptake in girls is more effective in reducing overall HPV infection levels than vaccinating boys; universal vaccination should be considered only when female uptake cannot be further increased. Further research is needed to estimate the benefit that men who have sex with men (MSM) may derive from a girls-only vaccination programme.

As a first objective towards predicting the short-term impact of HPV vaccination, we aimed to estimate the 'waiting time' distributions from HPV incidence to the development of precancerous (CIN2/3) lesions and to invasive cervical cancer. Preliminary results show a relatively short time from HPV infection to CIN2/3 lesions (3-5 years) but a large and variable time from CIN2/3 lesions to cervical cancer (> 25 years). The estimated 'waiting time' depends on assumptions of disease progression and screening behaviour, indicating that more research is needed on these topics. From our current insights, the first effects of HPV vaccination on the detection of precancerous lesions are not expected before

2023 (see also paragraph 4.12.6.2). A reduction in the number of cervical cancer cases due to vaccination will take much longer to observe.
To identify surrogate endpoints informative for assessing the extent of herd immunity obtained through HPV vaccination, we have started to evaluate the seroprevalence of type-specific antibodies against HPV in population-based studies. Although naturally occurring antibody levels are much lower than vaccine-induced titres, the age-dependent serological patterns clearly show an increase in the probability of seroconversion around the age of 20, coinciding with the peak incidence in HPV infection.

4.12.7 International developments

The quadrivalent HPV vaccine has been proven in recent years to be efficacious in preventing persistent infection and genital disease in females. Recently, a study done by Giuliano et al. showed that HPV vaccination has the potential to (besides females) reduce HPV-associated anogenital infection and disease in boys and men 16 to 26 years of age.[133] The results of this trial suggest that prophylactic vaccination of boys and men with quadrivalent HPV vaccine may reduce the incidence of for example condylomata acuminate. In the ITT population an efficacy of 60.2% (95% CI 40.8 -73.8) was seen and an efficacy against lesions related to HPV-6, 11, 16, or 18 was 90.4% (95% CI 69.2 to 98.1). In 2009, Gardasil has been FDA approved for use in males age 9 to 26 years for prevention of genital warts and anal cancer.[134]
The quadrivalent vaccine has also been proven effective for women >26 years old (*see section vaccine effectiveness*). The vaccine has been registered in Europe for this age group. However, the Food and Drug Administration (FDA) did not licence the quadrivalent vaccine for women aged >26 years.
Another recent publication shows the first effects of vaccination after the introduction of vaccination in 2008 in Australia.[135] They found a decrease in the incidence of high-grade cervical lesions in girls aged younger than 18 years. This decrease began soon after the introduction of the vaccination programme. In women aged 18–20 years, a decrease in incidence seems to have begun about 1.5 years after vaccine introduction. These results do have to be taken with caution since this study was an ecological study and did not link the cancer registry to the vaccination status of the women.

5 Future NIP candidates

5.1 Rotavirus infection

I.H.M. Friesema, W. van Pelt, A. Kroneman, W. Luytjes, J.M. Kemmeren, H.E. de Melker

5.1.1 Key points

- The rise in incidence of rotavirus associated gastroenteritis appears to continue in 2010.
- Rotavirus is the most important cause in case of hospitalisation due to gastroenteritis in children aged younger than 5 years.
- In 2010, G1P[8], G3P[8], and G2P[4] were most commonly found in the Netherlands.

5.1.2 Epidemiology

The Working Group Clinical Virology reports the number of rotavirus positive results weekly (see Appendix 2). In 2006, this number was much higher compared to the years before, followed by a drop in 2007. In 2008 and 2009 the numbers were again higher than in 2006. In 2010, the number of rotavirus positive monsters increased further. With the use of the ICD-codes 86-93, 5589 as reported in PRISMANT and the reports of the Working Group Clinical Virology an estimation of the hospital admissions can be made (see Appendix 2). In the age group younger than 5 years, three-quarters of the hospitalisations with these ICD-codes is thought to be caused by rotavirus.
The laboratory for Infectious Diseases and Perinatal Screening of the RIVM performs supplementary diagnostics on outbreaks that tested negative on a quick test or ELISA for norovirus and rotavirus at the regional laboratories.[136] In 2010, 441 of the 731 received samples tested positive for one or more viruses. Rotavirus was found in 66 samples (9%).

5.1.3 Pathogen

Since June 2008, the laboratory for Infectious Diseases and Perinatal Screening of the RIVM has participated in a European study (EuroRotaNet) on circulating serotypes of rotavirus. In 2010, 584 rotavirus-positive faeces samples were retested at the RIVM of which 556 (96%) tested positive and 551 could be typed.[137] The patients of the positive monsters sent to the RIVM were mainly aged 2 years (50%) or 3 years (23%), 17% was younger, 5% were aged 4-18 years and 4% were adults. 23% of the rotavirus-positive samples contained also one or more other viruses (norovirus, adenovirus, astrovirus or sapovirus). Almost half of the rotaviruses were G1P[8], a quarter was G3P[8], and one-sixth was of variant G2P[4]. In 2009, G4P[8] was the second most prevalent variant with 24%, in 2010 it was the fourth variant.
Results of EuroRotaNet showed for the years 2006-2009 that G1P[8] was predominant in Europe (48%) followed by G4P[8] (15%), G9P[8] (12%), G2P[4] (10%), and G3P[8] (4%).[138]

5.1.4 Adverse events

In the past year, no safety signals were identified for rotavirus vaccines. Several studies showed low reactogenicity and acceptable safety profile of the RIX4414 (Rotarix) oral suspension (liquid formulation) vaccine.[139-143] There was no

indication of clinically meaningful differences between the vaccine and placebo groups in terms of the overall reactogenicity and safety. Furthermore, a pilot study regarding rotavirus vaccine shedding in premature children showed infrequent solicited AEs among these children, confirming a good safety profile.[144] Vesikari et al.[145] showed that concomitant administration of the first doses of MenCC, DTaP-IPV-Hib and Rotateq was associated with a higher rate of vomiting and diarrhoea than concomitant administration of MenCC and DTaP-IPV-Hib, but that was not observed after the second concomitant administration. They concluded that the convenience of concomitant administration of Rotateq and MenCC may outweigh the additive effect of mostly mild AEs reported after the individual administration of each vaccine.
In addition to the discussion about the presence of porcine circovirus in rotavirus vaccines in the past years, Baylis et al.[146] showed that although PCV1 is present in Rotarix in a Benzonase resistant and thereby putatively encapsidated form, it is not infectious.

5.1.5 Current/ongoing research

The laboratory for Infectious Diseases and Perinatal Screening of the RIVM remains participating in EuroRotaNet to monitor circulating serotypes of rotavirus.
Several analyses have been made to determine the cost-effectiveness of rotavirus vaccination in the Netherlands, with inconsistent and varying results.[147-150] A new study investigated this topic again with extra attention given to the factors responsible for the differences in the previous studies.[151] Their conclusion was that inclusion of rotavirus vaccination in the Dutch NIP might be cost-effective depending on the cost of the vaccine and the impact of rotavirus gastroenteritis on quality of life (QALY). Factors associated with uncertainties in the calculations and explaining differences between the studies were differences in assumed underreporting, which factors were taken into account in the QALY calculations, inclusion of possible herd protection, and assumed mortality rate.

5.1.6 International developments

The standard RotarixTM (RIX4414) vaccine has to be reconstituted with a liquid calcium carbonate buffer prior to oral administration. This complicates vaccine administration and puts pressure on storage spaces as the vaccine and the buffer have to be stored separately. Therefore, a liquid formulation of RIX4414 vaccine has been developed and was evaluated in Finland.[142] The results suggested no significant differences between the two formulations regarding vaccine uptake, vaccine virus titre, and side effects.
Analyses using existing databases to evaluate the effect of rotavirus vaccination in a number of early introducer low-middle, middle and high income countries showed observed reductions that suggest that the proportion of diarrhoea caused by rotavirus might be greater than was estimated on the basis of prevaccine surveillance.[152] The postvaccination data indicate large reductions of all cause diarrhoea and rotavirus hospitalisations among children younger than 5 years, but also of rotavirus infections among age groups that were not vaccinated, suggesting herd effect. For example, hospitalisation of all-cause diarrhea declined with 30-45% in the not-vaccinated age groups in the United States[153], and a reduction of more than 50% of rotavirus hospitalisations in these age groups in Australia.[154] As only infants are vaccinated, these indirect beneficial effects implicate that infants act as the primary transmitters of infection. Nevertheless, also a shift towards strains less controlled by the current vaccines was seen: in areas vaccinating with Rotarix or RotaTeq an increase in

G2P[4] or G3P[8], respectively was seen[155-157], although a natural shift in strain -unrelated to vaccination- cannot be ruled out yet.

5.2 Varicella zoster virus (VZV) infection

E.A. van Lier, H.J. Boot, J.M. Kemmeren, W. Luytjes, I. Stirbu-Wagner, N.Y. Rots, H.E. de Melker

5.2.1 Key points

- No striking changes occurred in the VZV epidemiology in the Netherlands in 2010.
- The second cross-sectional population-based serosurveillance study (PIENTER 2) conducted in 2006/2007 confirmed the low age of VZV infection in the Netherlands compared to other countries.

5.2.2 Epidemiology

5.2.2.1 Incidence

The estimated number of patients with varicella and herpes zoster consulting a GP were obtained from the two sentinel surveillance networks of the Netherlands Institute for Health Services Research (NIVEL): the sentinel Continuous Morbidity Registration (CMR) and the Netherlands Information Network of General Practice (LINH) (Table 14).[158-160] Starting in 2008, the CMR has changed from registration on paper to electronic reporting, which could have resulted in underreporting of the number of varicella patients.[158] Therefore, we discontinued the CMR registration for varicella in 2011 and used data solely from the 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.[161] In contrast, the incidence of herpes zoster is stable over the years, which is consistent with the literature.[162] 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 24).[158-160]

Table 14 Incidence, per 100,000, of GP consultations due to varicella or herpes zoster in 2000-2010 (rounded off to tens)

Type	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Varicella*	200	240	320	270	250	190	300	210	(160)	(110)	(180)
Varicella**	-	-	190	160	200	130	260	230	290	180	210
Herpes zoster*	330	320	-	-	-	-	-	-	-	-	
Herpes Zoster**	-	-	320	330	310	350	370	310	340	360	360

*Continuous Morbidity Registration (CMR) Sentinel General Practice Network[158, 160]

**Netherlands Information Network of General Practice (LINH)[159]

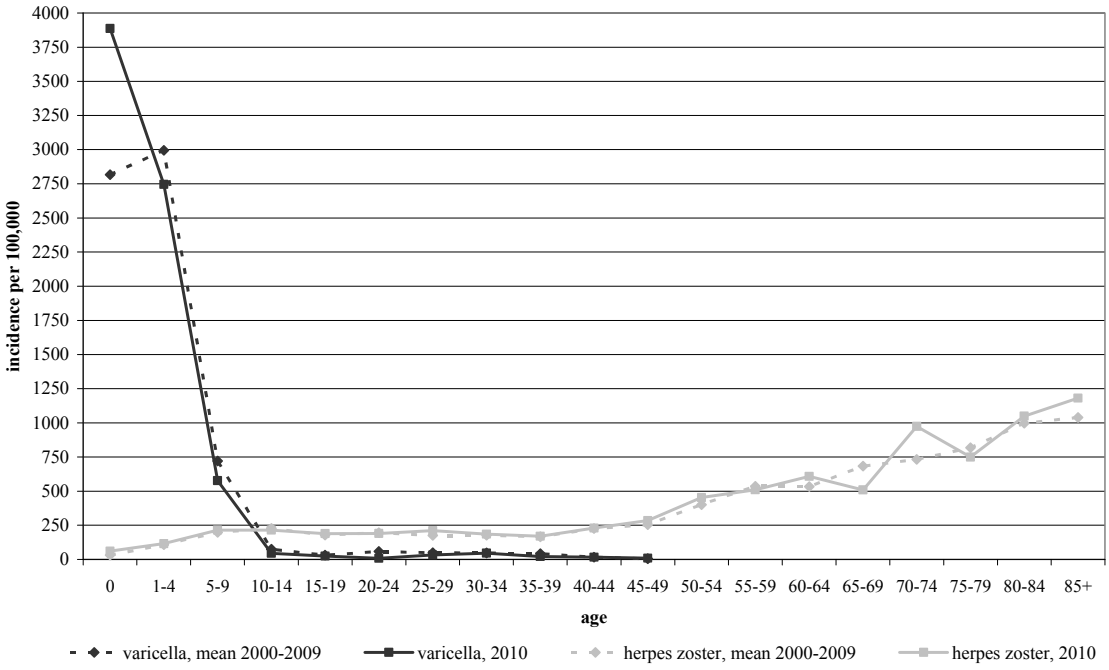

Figure 24 Incidence of GP-consultations per 100,000 for varicella and herpes zoster incidence in 2010 versus mean incidence in 2000-2009.[158-160] Note: varicella cases in persons older than 49 are only sporadically reported by GPs and are therefore not included.

5.2.2.2 Hospitalisation

The numbers of hospitalised patients 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)[163] and the incidence per 100,000 population is displayed in Table 15. Since 2006, the coverage of the National Medical Register has varied. Only clinical admissions were included (admissions for one day were excluded). The number of admissions can be higher than the number of hospitalised patients that is reported here because some patients were admitted more than once within the same year. The incidence of hospitalised patients with herpes zoster is – like the GP consultations – stable in the period 2000-2010. The incidence of hospitalised patients due to main diagnosis varicella is highest among 0-year-olds and for herpes zoster highest among the oldest age groups (Figure 25).

Table 15 Incidence per 100,000 of hospitalisations due to main and side diagnosis varicella or herpes zoster, 2000-2010 (Source: Prismant 2010)

Type	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Varicella	1.3	1.5	1.4	1.7	1.7	1.5	1.9	1.4	1.7	1.5	1.9
Herpes zoster	2.3	2.5	2.7	2.2	2.5	2.2	1.9	2.0	2.0	2.4	2.1

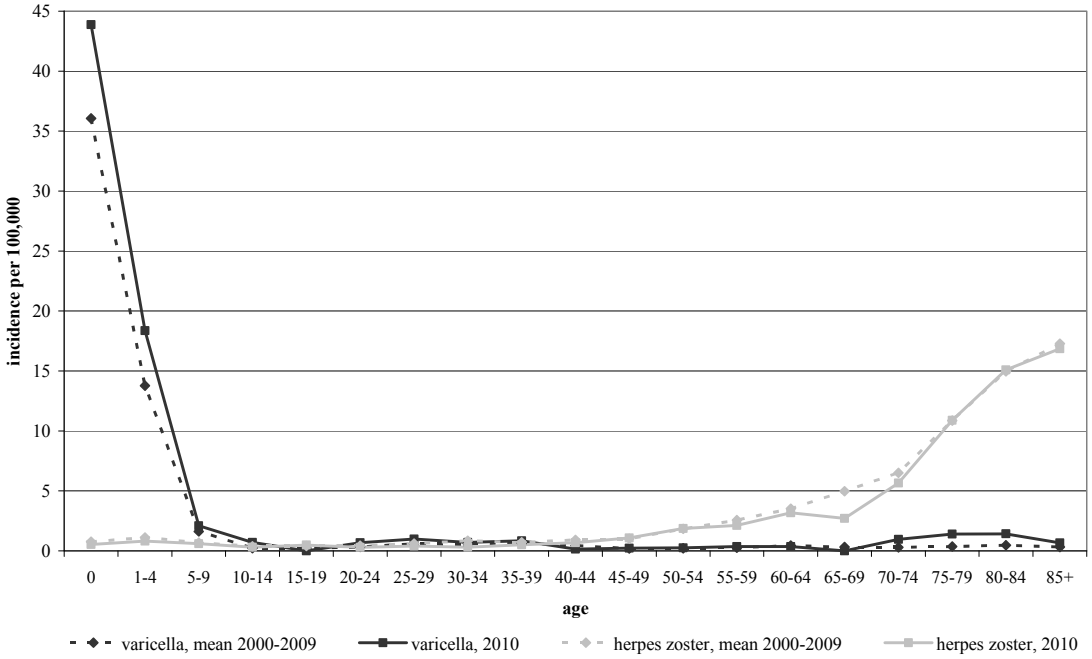

Figure 25 Incidence of hospitalised patients per 100,000 for main diagnosis varicella and herpes zoster in 2010 versus mean incidence in 2000-2009 (Source: Prismant, 2010)

If we define hospitalisation rate as the number of hospitalised patients divided by the number of GP consultations, we see that the hospitalisation rate is high among the youngest age groups and rises with age for varicella in particular (Figure 26).

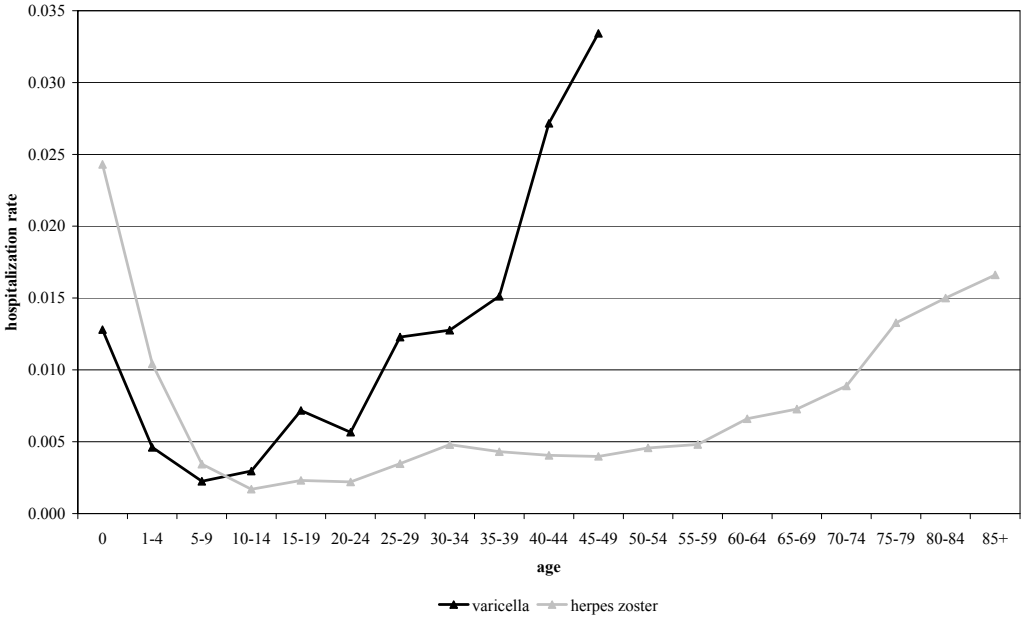

Figure 26 Mean hospitalisation rate 2000-2009 (number hospitalised patients (Source: Prismant, 2010)/number of GP consultations)[158-160] Note: varicella cases in persons older than 49 are only sporadically reported by GPs and are therefore not included.

5.2.2.3 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 16).[164] In 2010, there were two reported deaths with main cause of death varicella and 25 deaths with main cause of death herpes zoster.

Table 16 Number of deaths with main cause of death varicella or herpes zoster, 2000-2010 (Source: Statistics Netherlands)

Type	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Varicella	1	3	4	6	4	1	3	5	0	1	2
Herpes zoster	14	13	26	14	15	15	24	21	14	20	25

5.2.3 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 and 3 strains are most prevalent.[165] Although recombination of strains belonging to different clades has been reported (including the OKA-vaccine clade 2 strain)[165], 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.

5.2.4 Adverse events

5.2.4.1 Varicella vaccination

Rümke et al. published a study which generated safety data for two doses of MMRV vaccine administered according to dose schedules using the shortest permitted interval of 4 weeks versus a longer interval of 12 months in children aged 11-13 months.[165] Local and general reactogenicity results were similar for both groups except for a higher incidence of fever during 0-14 days post dose 1 in the MMRV-4 weeks group. A study of Vesikari et al. showed that meningococcal ACWY-TT can be co-administrated with MMRV without affecting safety profiles of either vaccines during the second year of life.[166] Administration of live attenuated varicella vaccine did not result in serious AEs in HIV-infected children[167], following allogeneic hematopoietic cell transplantation[168], or in health care workers.[169]

5.2.4.2 Herpes zoster vaccination

One study evaluated the safety of Zostavax administered concomitantly versus nonconcomitantly with Pneumovax 23.[170] It showed that the concomitant group reported a slightly lower proportion of clinical AEs than the nonconcomitant group, although this difference was not statistically significant. All six reported serious AEs were deemed not related to the study vaccine. The Cochrane Collaboration found in a systematic review that AEs at the injection site were more common among vaccine recipients than placebo recipients, but they were mild and resolved in a few days.[171] SAEs were rare. However, only one trial met their inclusion criteria, so the need for further studies is urged.

5.2.5 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.[172] An important source of additional information is the Interdisciplinary Processing of Clinical 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. In 2011, new data on the seroprevalence of VZV have become available (PIENTER 2 project 2006/2007), which provide information on the occurrence of varicella in the Dutch population. A preliminary analysis confirmed the low age of VZV infection in the Netherlands that was also found in PIENTER 1 (1995/1996) (Figure 27). Data from IPCI and PIENTER 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. In addition, experience with different vaccination schedules, both in clinical trials and after introduction in national immunisation programmes of different countries, will be evaluated to come to the most effective vaccination schedule for the NIP. This information will be used in cost-effectiveness analysis.

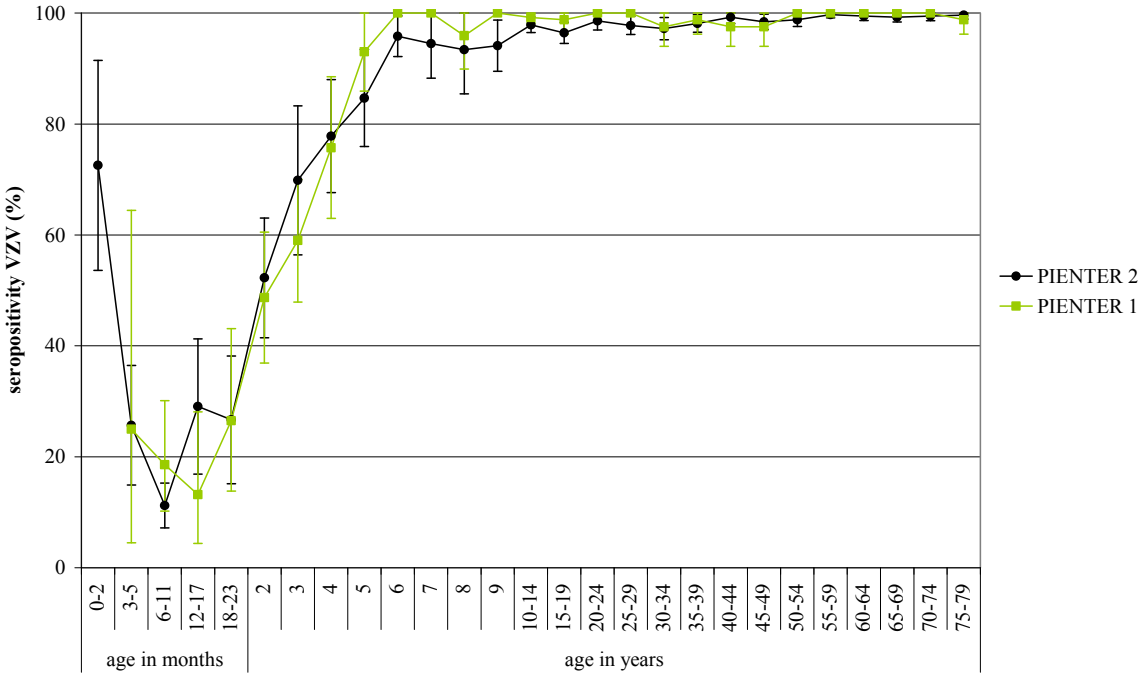

Figure 27 Seropositivity by age, PIENTER 1 (1995/1996) compared to PIENTER 2 (2006/2007)

5.2.6 *International developments*

Knuf et al. concluded that the immogenicity of the combined MMRV vaccine Priorix TetraTM was sustained three years post-vaccination. The anti-varicella antibody GMT in the MMRV group (MMRV*2) was two to three times higher than in the MMR + V group (MMR*2 + V*1) and the cumulative varicella breakthrough disease rate was 0.7% in the MMRV group and 5.4% in the MMR + V group.[173]

Since the implementation of a routine one-dose childhood varicella vaccination programme in 1995 (with recommendation of a routine second dose in 2006), the mortality rate attributed to varicella as the underlying cause declined by 88% compared with the prevaccine years in the United States.[174] A decline was

seen in all age groups but was highest among children and adolescents younger than 20 years (97%). Another study in the United States showed that there might be a stronger relationship between herpes zoster and family history of herpes zoster than reported before.[175] Furthermore, it seems that a genetic predisposition to herpes zoster is more frequently inherited along maternal lines.

A modelling study in England[176] suggested that a two-dose schedule (with a coverage of around 90% for the first and >70% for the second dose) is likely to reduce the incidence of varicella to very low levels. However, single dose programmes are expected to result in large numbers of breakthrough cases and vaccination at intermediate levels of coverage (70% for the first and 60% for the second dose) is expected to lead to an increase in adult varicella. The same study also suggested that although the increase in herpes zoster after introduction of a varicella childhood programme can be partly offset by vaccination of the elderly, the effectiveness of this strategy is limited (much of the zoster increase occurs in middle-aged adults, i.e. adults who are too young to be vaccinated by a programme targeted at the elderly (70 years)).[176]

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 in the Netherlands. One of the concerns is the feasibility of reaching a high vaccination coverage in the Netherlands, as varicella is usually seen as a benign disease. 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) due to diminishing exogenous boosting. The 'exogenous boosting hypothesis' strongly determines the cost-effectiveness of universal varicella vaccination. The conclusion in Belgium was that universal varicella vaccination (two-dose strategy with the first dose at the age of 1 year and a second dose at 4, 6 or 11 years) is possibly cost-effective (while zoster vaccination of 60–year-olds is probably not) but only in case the 'exogenous boosting hypothesis' is proven not to be correct.[177] So far in Europe, Germany (since 2004), Greece (since 2006), Latvia, Luxembourg (since 2009) and some regions of Italy and Spain have introduced universal varicella vaccination; some other European countries only vaccinate high-risk groups (http://ecdc.europa.eu/en/activities/surveillance/euvac/schedules/Pages/varicella.aspx and collected additional information[178]).

5.3 Hepatitis A

I.H.M. Friesema, L.P.B. Verhoef, W. Luytjes, J.M. Kemmeren, A. Lugner, A. Suijkerbuijk

5.3.1 Key points

- In 2010, the number of hepatitis A infections (262 cases) increased to the level of 2006 (269 cases; 2007-2009: 156-189 cases/year).
- In many developing countries with improved socioeconomic conditions, prevalence of hepatitis A is decreasing.
- In Belgium, a country with comparable hepatitis A epidemiology, it was demonstrated that both universal and adult vaccination would not be economically attractive. This would imply that vaccination would have similar unfavourable cost-effectiveness ratios in the Netherlands.

5.3.2 Epidemiology

In 2010, 262 cases of hepatitis A were reported in the Netherlands corresponding to 1.6 cases per 100,000 inhabitants. This is comparable to the

269 reported cases in 2006 (see Figure 28), but still lower than between 2000 and 2004 (375-701 cases per year). Between 1999 and 2010 the mean number of hospitalisations was 35, whereas the proportion of hospitalised hepatitis A cases of the total number of notifications increased from 4% in 1999 to 20% in 2010. In 2010, 52 cases (20%) were hospitalised, which is higher than previous years and may partly be explained by an outbreak occurring in 2010.[179] The mean age at infection increased from 17 in 1991 to 30 in 2010. Older patients experience a longer duration of hospitalisation stay than younger patients (more than 11 days for patients older than 65 compared to 5 days for patients up to 65, based on LMR data). Mortality caused by a HAV infection did not seem to increase. Since 1999 nine fatal hepatitis A infections have been registered (see Appendix 2).

About one-third of the cases were reported to be travel-related, which is lower than in previous years (43-54%). Morocco (15 cases; 5.7%), Egypt (14 cases; 5.3%) and Turkey (8 cases; 3.0%) were mentioned most. At least a quarter of the cases were secondary cases infected by closely related persons or MSM contacts. Food or water were implicated in 18% of the cases, including a national outbreak with semi-dried tomatoes as the potential source of infection.[179]

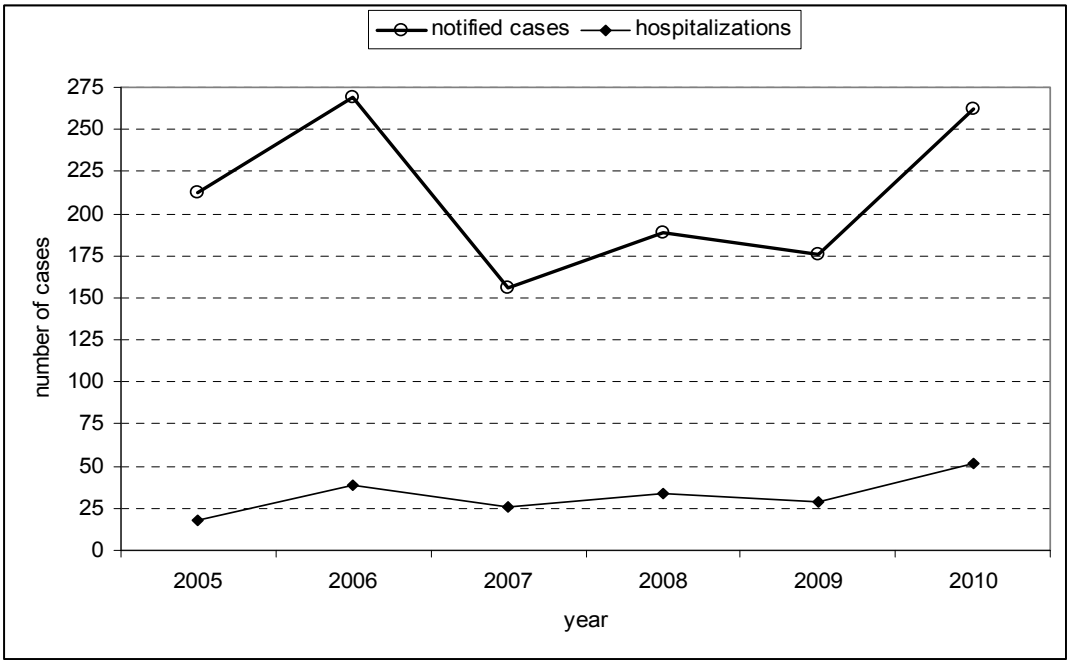

Figure 28 Number of reported and hospitalised cases of hepatitis A, 2005-2010

5.3.3 Pathogen

IgM-positive samples can be sent to the Laboratory for Infectious Diseases and Perinatal Screening of the RIVM for typing as part of the molecular surveillance of hepatitis A cases. In 2010 a total of 334 samples were tested, of which samples of 217 were positive and 211 (97%) could be typed, resulting in 78 unique sequences of which 27 clusters of 2 to 17 cases.[137]

5.3.4 Adverse events

A few studies were conducted to assess the safety of hepatitis A vaccines concomitantly given with other childhood vaccines. Trofa et al.[180] demonstrated

that two doses of HAV vaccine with the first dose administrated alone or coadministrated with DTaP and Hib vaccines in children 15 months of age, was well tolerated. Another study showed that HAV vaccine with MMR and varicella vaccines was safe in children less than 2 years of age.[181] Furthermore, HAV vaccine was well tolerated in children with HIV infection[182], and in children with juvenile idiopathic arthritis.[183]

5.3.5 Current/ongoing research

Initially, the typing of IgM-positive samples by the Laboratory for Infectious Diseases and Perinatal Screening of the RIVM was done for a period of two years, but is now continued for an indefinite period of time as it adds valuable data for the detection and follow-up of clusters and outbreaks. The results are linked to the reported cases, where possible, to combine the available information about microbiology and epidemiology. In case of a cluster with cases with dates of illness onset close together, mostly an outbreak investigation is started to find out what the cause was.

5.3.6 International developments

The socioeconomic status of a country is associated with prevalence of hepatitis A. In developing countries with improved socioeconomic conditions, prevalence of hepatitis A decreases.[184] Such a shift is currently affecting many regions of the world. Where nearly all children became infected at an early age, with the majority of the infections being asymptomatic and resulting in lifelong immunity, an increasingly large population of all ages now becomes susceptible to a hepatitis A infection. Besides the risk of outbreaks, the shift to older age groups results in increased clinical severity. As asymptomatic children probably represent the biggest source of infection, the WHO recommends areas of intermediate endemicity to consider universal childhood vaccination.[184] Existing programmes of universal childhood vaccination have shown to be effective and also provide herd immunity. In the Netherlands, the incidence of hepatitis A is classified as very low endemicity (< 5 cases/100,000/year). However, the population at risk is ageing which can lead to public health problems in the future as the chance of serious illness due to HAV is larger for adults and the elderly than in children.[185]

5.3.6.1 Cost-effectiveness

Since the introduction of an effective vaccine in the early nineties, universal and selective vaccination programmes have been proposed and implemented in various countries. Three studies evaluated cost-effectiveness of universal adult vaccination programmes.[186-188] All studies included the option to screen for antibodies against hepatitis A before vaccination as well as vaccinating all individuals regardless of susceptibility. These studies assessed that a vaccination strategy with and without screening would not be cost-effective; cost-effectiveness ratios were all above accepted thresholds.

Jacobs assessed that universal vaccination of 1- or 2-year-old children in all US regions would cost $1,400, according to Rein this would be $28,000 per QALY gained.[189, 190] Herd-immunity effects would be expected to produce substantial additional benefits.[191] Other studies in Chili, Argentina, Brazil, Israel and China revealed that starting a universal vaccination programme would be cost saving. In a recent Belgian study, however, universal infant vaccination at 95% uptake produced an ICER of €261,519 (direct costs per QALY gained).[186]

Numerous studies have been conducted to assess the cost-effectiveness of immunising older children and other target groups such as patients with hepatitis C, health care workers, food service workers, military, travellers, and

contacts of hepatitis A patients, with two doses of hepatitis A vaccine. Furthermore, several studies have assessed the cost-effectiveness of substitution of current hepatitis B vaccination programmes for combined HAV/HBV vaccination.

5.3.6.2 Implications for the Netherlands

The incidence of hepatitis A infections turns out to be one of the major determining factors for the cost-effectiveness of hepatitis A vaccination. In Belgium, a neighbouring country with comparable hepatitis A epidemiology, an extensive study, including transmission effects, demonstrated that both universal and adult vaccination would not be economically attractive.[186] As many factors affecting cost-effectiveness of vaccination are comparable between Belgium and the Netherlands, this could imply that vaccination would have similar unfavourable cost-effectiveness ratios in the Netherlands.

Given the low incidence of hepatitis A infections, targeted vaccination of risk groups as food handlers, patients with hepatitis C infection and health care workers, may work out less favourable in terms of cost-effectiveness in the Netherlands. With a relatively long incubation period of hepatitis A infections timely vaccination of household and other contacts can be an adequate alternative in order to effectively mitigate hepatitis A-outbreaks. Such an approach was proven to be cost saving when the primary case was located in a day care centre or school, and to have acceptable cost per symptomatic case prevented when vaccinating household contacts of cases.[192]

5.4 Meningococcal serogroup B disease

T.M. van 't Klooster, S.C. de Greeff, G.A.M. Berbers, G.P.J.M. van den Dobbelsteen, J.M. Kemmeren, H.E. de Melker, L.M. Schouls

5.4.1 Key points

- The incidence of meningococcal B disease had decreased further in 2010.
- A meningococcal B vaccine has been applied for a license (Bexsero, Novartis).

5.4.2 Epidemiology

Since 2001 the number of patients with meningococcal B disease has been decreasing, as can be seen in Figure 29 and Table 17. In 2010 the number of cases had decreased to 110. The reason for this decreased incidence remains enigmatic. Possibly, natural fluctuation may explain this decreasing trend.

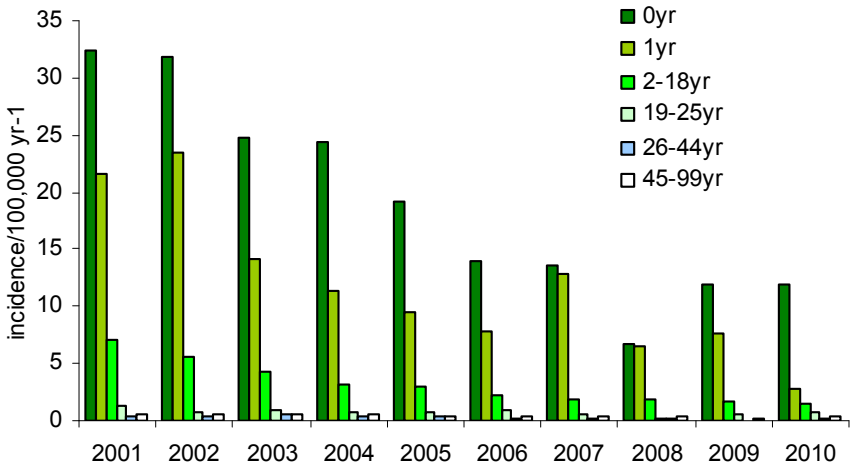

Figure 29 Age-specific incidence of MenB disease by year, 2001-2010

Table 17 Absolute number of patients with MenB disease per age-category from 2001-2010

Age (Yrs)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
0	69	66	50	47	37	26	25	12	22	22
1	45	50	29	23	19	15	24	12	14	5
2-18	236	195	142	110	103	76	64	65	56	47
19-25	19	11	14	8	11	12	7	3	8	11
26-44	20	21	21	13	15	9	8	5	3	4
44-99	38	42	37	33	27	20	21	26	14	21
Total	**427**	**385**	**293**	**234**	**212**	**158**	**149**	**123**	**117**	**110**

5.4.2.1 Immune surveillance

There is currently no vaccination against MenB and consequently no immune surveillance studies have been performed.

5.4.3 Pathogen

There are no indications that the properties or the composition of the population structure of this pathogen has changed.

5.4.4 Adverse events

Two phase I trials assessed the safety of experimental MenB vaccines. Overall the vaccines were well tolerated, and no vaccine-related serious AEs were reported.[193, 194] There was no evidence of residual endotoxin activity in terms of increased temperatures or with blood cell counts. Injection site reactions were not dose related and appeared to be worse in those receiving aluminium hydroxide adjuvant.[193]

Three phase II trials assessed the tolerability of recombinant MenB vaccine with or without the outer membrane vesicle from the New Zealand epidemic strain. Both vaccines were generally well tolerated[195, 196], although the rMenB+OMV vaccine (Bexsero) was associated with greater proportions of vaccinees with local reactions of induration and tenderness and local severe reactions.[195] Kimura assessed the safety of Bexsero and MenACWY-CRM administered concomitantly in laboratory workers.[197] Rates of solicited reactions were lower after MenACWY-CRM than after Bexsero. However, it is possible that the open-label study design confounded the results.

In three randomised studies, Toneatto showed that compared with rMenB, rMenB plus outer membrane vesicles from the Norwegian outbreak strain appeared somewhat more reactogenic.[198] Both investigational vaccines were more reactogenic than the licensed vaccines. However, they concluded that based on the reactogenicity, both vaccines were promising candidates for further investigation.

5.4.5 Current/ongoing research

For a broad coverage against a variety of meningococcal B serosubtypes, a multivalent PorA outer membrane vesicle (OMV) vaccine has been developed by the NVI/RIVM to be used for infants. Recently, we developed a new generation NonaMen consisting of OMVs of three different trivalent Neisseria meningitidis strains: RL16215, RL 10124 and RL1416. Beside the nine different PorA's (defining the serosubtype), lpxL1 and rmpM mutations were introduced in these new strains. Deletion of lpxL1 attenuated the LPS toxicity, while preserving the adjuvant activity needed for the immune response. In addition, rmpM deletion mutants were found to have a loosely attached outer membrane resulting in an increased OMV release and consequently in a higher OMV yield. Non-clinical batches for immunogenicity and toxicity studies have been prepared. New generation NonaMen has been shown to be immunogenic in mice and rabbits. At the moment, the focus of the project is on preparing GMP batches for clinical studies.

5.4.6 International developments

Novartis has applied for a license for their meningococcal B vaccine for infants (Bexsero). This multicomponent vaccine, 4CMenB, contains three primary recombinant protein antigens: factor H binding protein (fHbp), Neisserial heparin binding antigen (NHBA) and Neisserial adhesin A (NadA) plus OMV from strain 44/76, which was the primary antigen in vaccine that used to control the outbreak in New Zealand (PorA P1.7-2,4, MeNZB).
The Pfizer MenB vaccine candidate is a bivalent vaccine composed of two variants of LP2086 also known as factor H binding protein. A phase III, randomised, placebo and active-control, observer-blind trial to assess the safety, tolerability and immunogenicity given in healthy subjects aged ≥ 11 to < 26 years is carried out in Poland at the moment. The target group for this vaccine is adolescents and not infants.

5.5 Meningococcal non-serogroup B and C types

T.M. van 't Klooster, S.C. de Greeff, G.A.M. Berbers, G.P.J.M. van den Dobbelsteen, J.M. Kemmeren, H.E. de Melker, L.M. Schouls

5.5.1 Key points

- Serogroup Y has recently emerged in some countries.

5.5.2 Epidemiology

Since 2001 the number of patients with meningococcal serotype W135 disease has been decreasing, as can be seen in Figure 30 and Table 18. In 2010 the number of meningococcal serotype Y cases was 11 (Figure 30 and Table 19).

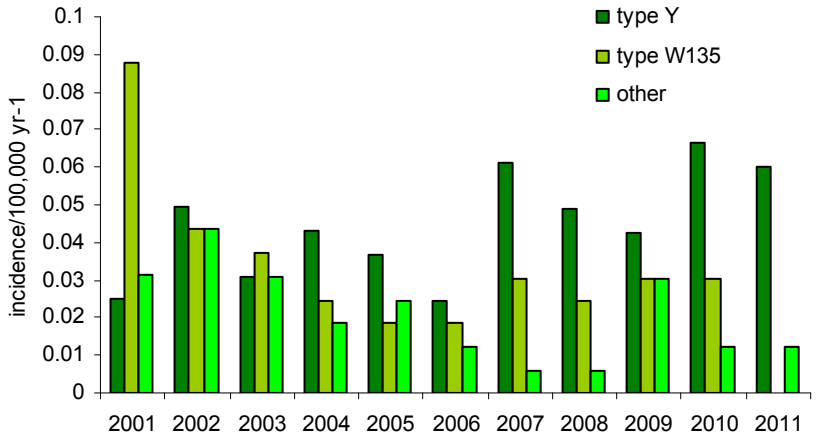

Figure 30 Incidence of Meningococcal non-B and non-C types by year, 2001-July 2011

Table 18 Absolute number of patients with Men W135 disease per age-category from 2001-July 2011

Age (Yrs)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011[a]
0	3	1	0	0	1	0	1	0	0	0	0
1	0	0	3	0	0	1	1	1	1	1	1
2-18	3	2	1	0	1	1	1	0	1	2	2
19-25	1	0	0	0	0	0	0	1	0	0	0
26-44	3	1	0	0	0	1	1	0	1	0	0
44-99	4	3	2	4	1	0	1	2	2	2	2
Total	**14**	**7**	**6**	**4**	**3**	**3**	**5**	**4**	**5**	**5**	**5**

[a] Until July

Table 19 Absolute number of patients with Men Y disease per age-category from 2001-July 2011

Age (Yrs)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011[a]
0	0	0	1	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0	1	0
2-18	0	1	1	3	0	0	0	0	1	1	4
19-25	0	2	0	0	0	0	2	1	1	2	1
26-44	1	0	1	0	0	0	0	1	0	2	2
44-99	3	5	2	4	6	4	8	6	5	5	3
Total	**4**	**8**	**5**	**7**	**6**	**4**	**10**	**8**	**7**	**11**	**10**

[a] Until July

5.5.3 *Pathogen*

There are no indications that the properties or the composition of the population structure of these pathogens has changed.

5.5.4 *Adverse events*

See paragraph 4.9.5.

5.5.5 Current/ongoing research

The RIVM is collaborating with a research group in Sweden to analyse the isolates of emerging serogroup Y meningococci by molecular typing.

5.5.6 International developments

Kriz et al. recently published a review paper on the changing epidemiology of meningococcal disease in Europe. In summary this paper describes that the epidemiology of meningococcal disease is subject to constant change. Epidemics caused by serogroups A and B have occurred worldwide and outbreaks associated with serogroup C occurred in the 1980s and 1990s. Serogroup W135 disease was observed in the 1970s and recently serogroup Y has emerged in Scandinavia, the UK and the Czech Republic. Although the number of MenY disease incidences is small the increase is significant and needs careful monitoring. The authors suggest that the new multivalent polysaccharide ACWY conjugate vaccine may play a role in light of the increased MenY incidence.[199]

The vaccination campaign with the MenA conjugate vaccine (MenAfriVac) in the African meningitis belt, where from December 2010 within a half year up to 20 million people have been vaccinated in Burkina Faso, Mali and Niger, has already reduced the number of MenA cases enormously. Another 35 million vaccinations are planned this year in Nigeria, Kameroen and Tsjaad.

Currently, three polyvalent meningococcal conjugate vaccines (ACYW) have been developed for United States and European markets. Two are licensed; Menactra (Sanofi) is licensed in the US and Menveo (Novartis) in the US and Europe. Menveo is used to protect adults and adolescents aged 11 years and above against invasive disease caused by four groups of the bacterium *N. meningitidis* (A, C, W135, and Y). Menactra, a polysaccharide Diphtheria Toxoid Conjugate Vaccine, is indicated for active immunisation to prevent invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, Y and W-135 and is approved for use in individuals 9 months through 55 years of age. GlaxoSmithKline has submitted an application for a similar product in Europe. Licensure of these vaccines is based on non-inferiority clinical trials comparing fourfold rises in SBA titers after immunisation with either the conjugate or the polysaccharide vaccine.

6 Other possible future NIP candidates

M.C. van Blankers, G.P.J.M. van den Dobbelsteen, W. Luytjes, N.Y. Rots

The aim of this chapter is to update information with regard to vaccines for infectious diseases that are tested in clinical trials and are relevant for the Netherlands. New combination vaccines in development are not included in this chapter.

6.1 Respiratory Syncytial Virus (RSV)

Respiratory Syncytial Virus (RSV) is the leading cause of lower respiratory tract disease in infants and young children. Although RSV infections typically cause mild illness, serious disease can occur and is associated with symptoms as bronchiolitis and pneumonia, requiring hospitalisation, primarily of children under 6 months of age. Particularly at risk of severe disease after RSV infection are premature infants and infants with congenital heart disease (CHD) or bronchopulmonary dysplasia (BPD). Later in life, RSV causes primarily, sometimes severe, upper respiratory tract disease, but immunocompromised individuals, persons with congenital heart disease and the elderly are additional high-risk groups for lower respiratory tract disease. An effective vaccine might reduce the high burden of disease caused by RSV, but is not available yet.

RSV infects virtually every child by the age of 2. The epidemiology of RSV shows a seasonal incidence similar to influenza, with an incidence peak in the winter months. However, the RSV season on average starts 1.5 -2 months earlier than the influenza season.
In children, 1-2% of RSV-infections leads to pneumonia and bronchiolitis requiring hospitalisation. RSV-induced bronchiolitis may lead to mild and severe episodes of recurrent wheezing in infancy and asthma in 8-70% of cases. In school-age children, wheeze is no longer associated with a history of RSV-hospitalisation. The estimated (Meijboom et al., submitted) annual incidence per 100,000 of GP visits and hospitalisations for children under one year of age are 28,738 and 1,623 respectively. In the elderly, little data on morbidity is available. Based on a UK study[200] it was estimated that in the Dutch population of 65 years and over, assuming that ~19% of this population are high-risk persons and the rest of the elderly are healthy elderly, the annual incidence per 100,000 persons of RSV infections is 12,146, leading to 2488 GP visits and 541 hospitalisations (manuscript in preparation).
RSV mortality in children is primarily observed in the youngest children, age < 12 months. RIVM reports a mortality rate of 0.03 per 100,000 for the total population corresponding to a total number of 4.5 deaths per year due to RSV (equal to 2.78 per 100,000 infants 0-12 months of age). This is in line with estimations from the UK, where RSV incidence patterns are similar to those in the Netherlands. In the UK, excess mortality has been estimated at 2.9 deaths per 100,000 infants per year. In the elderly this number is estimated to be much higher: 120 per 100,000 corresponding to a total number of more than 3000.
Currently, severe RSV infection can only be treated by mechanical ventilation or nasogastric feeding. Antiviral drugs such as ribavirin are indicated only in infants with a compromised immune system, but the efficacy is questionable. Premature infants born just before or during the RSV season are prophylactically treated

with palivizumab, but its effectiveness is 50% at most and the treatment is expensive.
Thus, a vaccine should be available that at least protects infants at risk. As the majority of hospitalisations occur before the age of 6 months, this vaccine should induce protective immunity at a very early age. Currently, two phase I vaccine trials against RSV infection in infants are running, one with a live attenuated temperature sensitive mutant (MedImmune) and one with a chimaeric RSV/PIV3 recombinant (MedImmune). No results are known yet and should the trials be successful, introduction of these vaccines to the market is not expected within the next five years. RIVM plans to test its recombinant live attenuated vaccine in the clinic by the beginning of 2013, in a programme that is expected to take four years.

6.2 Tuberculosis (TB)

Tuberculosis is the world's second leading cause of mortality and morbidity. More than two billion people, equal to one-third of the world's population, are infected with TB bacilli, the microbes that cause TB. One in ten people infected with TB bacilli will become sick with active TB in their lifetime; people with HIV are at much greater risk. The vast majority of TB deaths –approximately two million people each year - occur in the developing world.
The TB incidence in the Netherlands was 6.5 patients per 100,000 persons in 2010, in 2009 the numbers were slightly higher, 7.0 per 100,000 persons (KNCV Tuberculose fonds). The majority (70%) concerns first generation immigrants.
The only TB vaccine (BCG-attenuated Bacille Calmette Guérin) used in the world today was developed over 80 years ago. A TB vaccine is especially important in areas of the world where TB is highly prevalent and the chances of an infant or young child becoming exposed to an infectious case are high. Although BCG is effective in protecting infants against childhood forms of the disease, the protection of adults and adolescents is suboptimal since BCG does not reliably prevent against pulmonary tuberculosis disease, the most common form of TB, in these age groups.
Research consortia involving both research institutes and pharmaceutical companies are developing different new TB vaccines. They are currently performing phase I or II clinical trials. RIVM/vaccinology researchers are participating in an EU consortium NEW TBVAC also developing an improved TB vaccine.

6.3 HIV/AIDS

The WHO estimates that since the start of the epidemic, HIV has infected more than 60 million men, women and children and AIDS has cost the lives of nearly 20 million adults and children. Despite the intense international response to the HIV/AIDS pandemic, HIV continues to spread, causing more than 14,000 new infections every day, 95% of which are in the developing world. Today AIDS is the leading cause of death in Africa, and the fourth one worldwide. In 2010, 1256 HIV-infected persons in care were newly registered in the national database of the HIV treatment centres (SHM); 826 of them were diagnosed in 2010. As of December 2010, a total of 17,850 HIV patients in medical care had been recorded in the Netherlands. The proportion of MSM among the newly diagnosed remained stable in 2010 (66%).[73]
The urgent need to accelerate the development of an AIDS vaccine prompted the United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) to join forces in establishing the new HIV Vaccine Initiative (HVI) to boost HIV/AIDS vaccine efforts.

A six-year collaborative HIV vaccine trial (incl. Sanofi-Pasteur) in Thailand, completed in 2009, has demonstrated that an investigational HIV vaccine regimen was safe and modestly effective in preventing HIV infection but did not protect those at highest risk of HIV. This is the first concrete evidence, since the discovery of the HIV virus in 1983, that a vaccine against HIV is potentially feasible. Other vaccine candidates are currently being tested in phase I or II clinical trials by GSK (F4/AS01) and Crucell (Ad26.ENVA.01/ Ad35-ENV).

6.4 Hepatitis C

Hepatitis C virus (HCV) is a virus that infects the liver. Most people who are infected develop persistent infection. A proportion of people (20-50%) develop progressive liver disease leading ultimately to liver cirrhosis, liver failure and hepatocellular carcinoma. HCV is globally distributed and it is estimated that up to 170 million people (3% of the world's population) are infected worldwide. Hepatitis C is transmitted via infected blood. In Western Europe and North America less than 1% of the population is infected and infection is largely confined to at risk populations including those that received blood transfusions before the screening of infected blood products and intra-venous drug users. Sexual transmission and perinatal transmission is unusual occurring in approximately 5% of cases. In 20% of people no cause of infection can be established (WHO).

A vaccine that prevents and treats HCV infection is urgently required. The target population would be at-risk groups in developed countries and the entire population in many developing countries. No such vaccine currently exists, but a number of approaches are currently in development. One of the major challenges facing the development of a vaccine for HCV is the high degree of genetic diversity that is exhibited by the virus, estimated to be tenfold higher than that seen in HIV. Other factors that have hindered vaccine development for HCV include the lack of an accessible animal model and the fact that the virus cannot be easily grown in the laboratory.
Several companies (Intercell/Romark Laboratories L.C, GlobeImmune and others) are currently testing therapeutic vaccines in clinical trials.

6.5 Hospital acquired infections

Hospital-acquired infections are a major concern for public health in many industrialised countries and cause significant annual costs to the healthcare systems.

6.5.1 Clostridium difficile (CD)

Clostridium difficile is a major public health concern in North America and Europe. *C. difficile* rarely causes infections in healthy persons but is a significant threat for patients with disruption of their intestinal flora by antibiotics, especially in healthcare settings, or with immunocompromising conditions. It is one of the leading causes in hospitals of infectious diarrhea in adults, particularly the elderly. The epidemiology of *C. difficile* infections (CDI) has been increasing at an alarming rate since 2003, initially driven by the emergence of a highly virulent strain, PCR ribotype 027. There is currently no vaccine available. In the EU the healthcare costs related to CDI are estimated at around three billion euros per year (source: CDC, ECDC). In the Netherlands in 2008, the incidence rate of CDI was 18 per 10,000 hospitalisations in the 14 hospitals participating in a continuous surveillance. During this period, 1867 cases were reported by 63 hospitals.[201]

Sanofi Pasteur has developed a toxoid-based candidate vaccine against *C. difficile*, a phase II study is under way. The vaccine developed by Novartis in collaboration with Intercell is being tested in a phase I trial. While the target indication for both vaccines is prevention, these trials — with recently infected patients — aim to provide early proof-of-concept of a vaccine approach for the prevention of recurring infection.

6.5.2 Staphylococcus aureus

Staphylococcus infections, including methicillin-resistant *Staphylococcus aureus* (MRSA), occur most frequently among persons in hospitals and healthcare facilities (such as nursing homes and dialysis centres). In the Netherlands, the incidence rate in hospitals is 1% and in the general population it is 0.13% which is low compared with other EU countries. MRSA is responsible for several difficult-to-treat infections in humans because the bacterium is resistant to a large group of antibiotics, including penicillins (i.e. flucloxacilline, methicilline and oxacilline). MRSA is one of the leading causes of nosocomial pneumonia and surgical site infection and the second leading cause of nosocomial blood stream infections.
Several companies (Sanofi-Pasteur together with Intercell; Pfizer) are developing a prophylactic vaccine against Staphylococcus, including MRSA. The vaccine candidate of Pfizer is comprised of *S. aureus* capsular polysaccharide serotypes 5 and 8 conjugated to CRM197 and the recombinant surface-expressed MSCRAMM protein, clumping factor A. Results of the phase I trial showed that the vaccine elicited a positive immune response to each of the three components.

6.5.3 Pseudomonas aeruginosa

Most serious *Pseudomonas aeruginosa* infections occur in hospitalised and critically or chronically ill patients -primarily affecting the respiratory system in susceptible individuals and are a serious clinical problem due to their resistance to antibiotics. No incidence figures are available for the Netherlands.
A vaccine developed by Novartis together with Intercell is based on antigens derived from two outer-membrane proteins from *P. aeruginosa*. The vaccine was found to be highly immunogenic at all dose levels tested and has generated strong humoral responses even in intensive care patients, who have a high risk of immune suppression. There were no critical safety findings in this phase II study (Intercell website).

6.6 Infections transmitted from mother to newborn child

6.6.1 Group B Streptococcus (GBS)

Infection with Group B Streptococcus (GBS), also known as *'Streptococcus agalactiae'* and more colloquially as Strep B and group B Strep, can cause serious illness and sometimes death, especially in newborn infants, the elderly, and patients with compromised immune systems. Group B Streptococcus is part of normal flora of the gut and genital tract and is found in 20-40% of women. In the Netherlands around 20% of all pregnant women are carrying GBS. It is estimated that 50% of the children of these carrying mothers are colonised after birth. Approximately 1% of these children develops an infection. Mortality under these infected children is 5 per 100.[202] Overall incidence of neonatal GBS-sepsis is estimated to be between 0.4 and 1.9 per 1000 live birth. GBS infection may be harmful to both mother and the baby itself. Infection of this organism may result in neonatal death due to severe neonatal infection. It may also occasionally result in maternal death by causing upper genital tract infection

which progresses to septicemia. Carriage of the organism is asymptomatic. Newborn GBS disease is separated into early-onset disease occurring on living days 0–7 and late-onset disease which starts on days 7–90. Early-onset septicemia is more prone to be accompanied by pneumonia, while late-onset septicemia is more often accompanied by meningitis.
Novartis is currently in phase I/II clinical trials with a conjugate vaccine against GBS.

6.6.2 Cytomegalovirus (CMV)

CMV causes a spectrum of disease syndromes in children and adults. CMV is a cause of mononucleosis in immunocompetent individuals and is a well-known cause of serious morbidity and sometimes fatal infections in immunocompromised patients, especially recipients of solid-organ or hematopoetic cell allografts and individuals with advanced AIDS. CMV has been estimated to be the leading infectious cause of damage to the developing fetus in utero in the United States and in Europe as well as other developed areas of the world. Incidence of congenital CMV infection is low with 1 in 1000. Infection is associated with a range of clinical manifestations, but relatively few infected infants are severely ill at birth. More than 90% of CMV infected infants are asymptomatic but they excrete the virus. Of CMV infected women 40-50% will infect their unborn child. Roughly 10% of the infected children will experience severe neurological abnormalities such as microcephaly, sensory neural hearing loss, mental retardation, encephalitis or seizures.
GSK, Sanofi Pasteur and Novartis in collaboration with Alphafax have CMV vaccines in early clinical development.

6.7 Norovirus

Norovirus infection, more commonly known as the ‘stomach flu’, is the most common cause of acute gastroenteritis. Norovirus infections occur year round, but tend to increase in cooler months. Outbreaks can occur in institutional settings, such as schools, child care facilities, and nursing homes. The virus infects persons of all ages, but is most problematic in the pediatric and geriatric populations where infection can lead to hospitalisation, morbidity and even death. In the Netherlands each year approximately 4.5 milion inhabitants suffer from stomach flu, almost half a million cases were caused by norovirusses (RIVM). Ligocyte Pharmaceuticals, Inc, is developing a bivalent Virus-Like Particle (VLP) norovirus vaccine adjuvanted with monophosphoryl lipid A (MPL) and Aluminum Hydroxide (AlOH), which has been tested in adults in a phase I, randomised controlled dose escalation, safety and immunogenicity trial.

6.8 Others

Vaccines in development but not relevant for the Netherlands due to low disease incidence are vaccines against Dengue, Malaria, Japanese encephalitis and West Nile virus. In case of increased incidence numbers these vaccines will be evaluated for introduction in the NIP.

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Appendix 1 Vaccine coverage for infants targeted for HBV vaccination in the NIP, birth cohorts 2003-2010

Birth cohort	Indication	Vaccination	Number eligible	Number vaccinated	Coverage
2010	D (mother is HBsAg+)	Hep B-0	538[c]	533	99,1%[a]
2009	D (mother is HBsAg+)	Hep B-0	553	515	93,1%
2008	D (mother is HBsAg+)	Hep B-0	521	490	94,0%
2007	D (mother is HBsAg+)	Hep B-0	574	512	89,2%
2006	D (mother is HBsAg+)	Hep B-0	554	466	84,1%
2008	D (mother is HBsAg+)	Hep B completed	534	516	96,6%
2007	D (mother is HBsAg+)	Hep B completed	568	552	97,2%
2006	D (mother is HBsAg+)	Hep B completed	550	526	95,6%
2005	D (mother is HBsAg+)	Hep B completed	494	481	97,4%
2004	D (mother is HBsAg+)	Hep B completed	587	542	92,3%
2003	D (mother is HBsAg+)	Hep B completed	596	538	90,3%
2008	E (parent(s) migrant)	Hep B completed	37.392	35.432	94,8%
2007	E (parent(s) migrant)	Hep B completed	36.570	34.456	94,2%
2006	E (parent(s) migrant)	Hep B completed	36.235	33.669	92,9%
2005	E (parent(s) migrant)	Hep B completed	36.211	32.859	90,7%
2004	E (parent(s) migrant)	Hep B completed	36.404	32.275	88,7%
2003	E (parent(s) migrant)	Hep B completed	34.410	29.817	86,7%
2008	DS (Down syndrome)	Hep B completed	88[b]	83	94,3%

a. Coverage at age three days. Coverage at age 14 days: 100%

b. This is the number registered with Down syndrome (DS) in Præventis. This is only 30% of the estimated 297 children with DS born in 2008

c. The number of eligible children (538) is 0.29% of the 2010 birth cohort (n=184,397). The estimated antenatal prevalence in 2008 was 0.33% (609 of 184,634 infants)[74]

Appendix 2 Mortality and morbidity figures per disease from 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

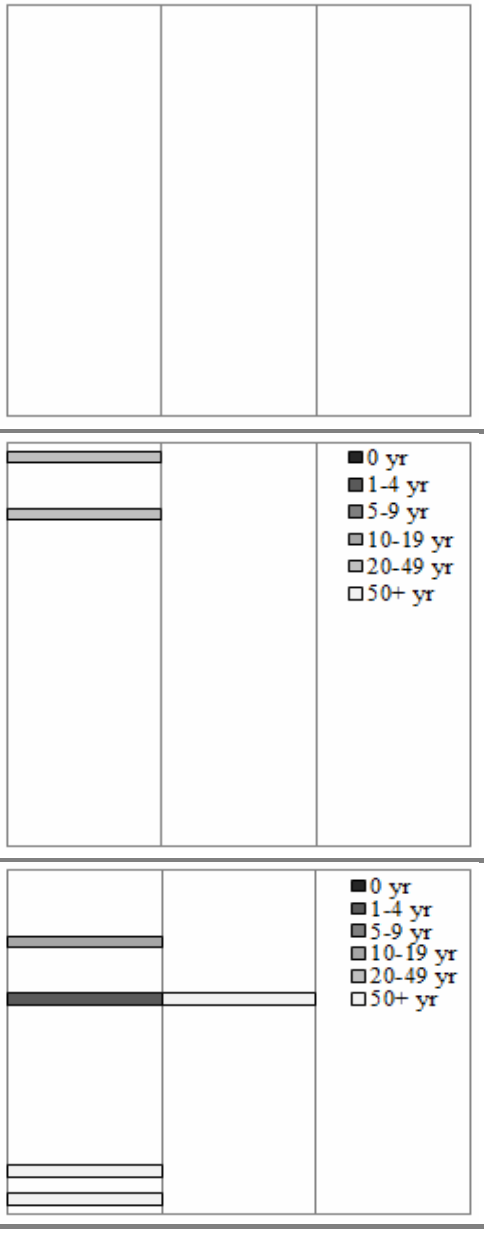
Data on notifications were retrieved from:
http://rivm.nl/Onderwerpen/Ziekten_Aandoeningen

Data on hospitalisations were retrieved from the National Medical Register, Prismant Utrecht. Only main diagnoses were included. Multiple hospitalisations per year of the same patient were excluded. For rotavirus an estimation of the hospital admissions is made with the use of the ICD9-codes 86-93 and 5589.

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 data from virological laboratories of the Dutch Working Group for Clinical Virology.

Diphtheria **ICD9 032** **ICD10 A36**

		Age (Years) 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	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
Notifications	1997	0	0	0	0	1	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	1999	0	0	0	0	0	0	0
	2000	0	0	0	0	0	0	0
	2001	0	0	0	1	0	0	1
	2002	0	0	0	0	0	0	0
	2003	0	1	0	0	0	1	2
	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	1	1

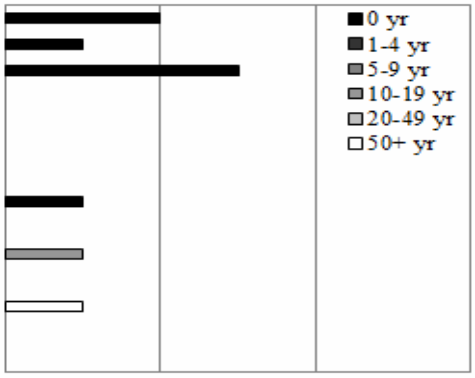


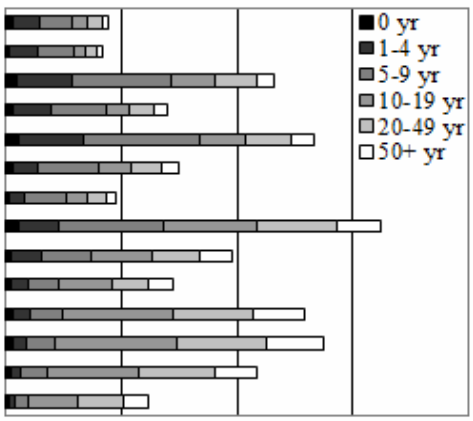
	Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total	N
2000	0	0	0	0	0	0	0	
2001	0	0	0	0	0	1	1	
2002	0	0	0	0	0	0	0	
2003	0	0	0	0	0	0	0	
2004	-	-	-	-	-	-	1	
2005	0	0	0	0	0	0	0	
2006	0	0	0	0	0	0	0	
2007	0	0	0	0	1	0	1	
2008	0	0	0	0	0	0	0	
2009	0	0	0	0	0	0	0	
2010	0	0	0	0	0	0	0	

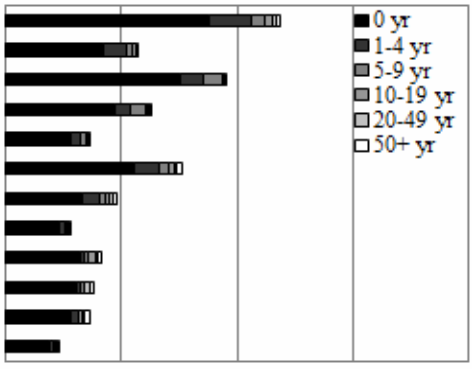
Isolates

Pertussis **ICD9 033** **ICD10 A37**

		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
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
	2010	0	0	0	0	0	0	0
Notifications	1997	213	705	821	379	420	126	2664
	1998	134	714	921	316	310	108	2503
	1999	307	1447	2526	1153	1084	447	6964
	2000	211	976	1460	564	648	363	4222
	2001	343	1676	3011	1169	1207	587	7993
	2002	198	666	1540	856	810	417	4487
	2003	126	372	1085	557	464	243	2847
	2004	363	1007	2745	2387	2091	1133	9726
	2005	183	783	1286	1567	1207	842	5868
	2006	141	469	785	1353	981	622	4351
	2007	189	450	842	2882	2056	1327	7746
	2008	194	345	776	3128	2325	1477	8245
	2009	162	262	650	2400	1964	1061	6499
	2010	113	165	345	1266	1189	637	3715
Hospitalisation	1999	352	73	24	12	8	5	474
	2000	171	37	12	5	0	5	230
	2001	302	40	33	1	2	3	381
	2002	190	25	27	4	3	3	252
	2003	114	16	9	2	2	3	146
	2004	224	42	15	11	3	12	307
	2005	134	29	11	7	4	7	192
	2006	95	7	2	3	2	5	114
	2007	129	7	8	11	5	8	168
	2008	125	6	5	2	7	9	154
	2009	113	13	1	5	6	8	146
	2010	77	6	2	2	2	5	94

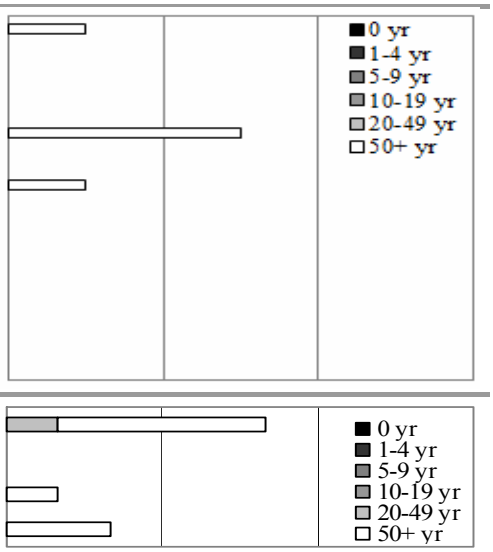






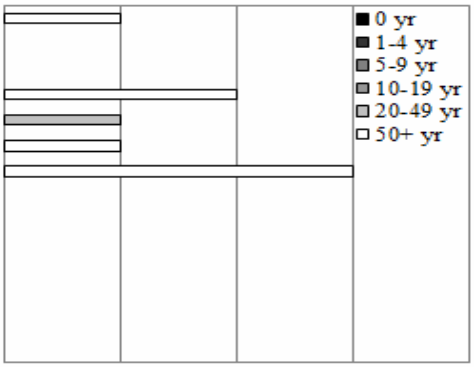
Tetanus **ICD9 037, 7713** **ID10 A33-35**

		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	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
	2010	0	0	0	0	0	0	0
Notifications	1997	0	0	0	0	1	4	5
	1998	0	0	0	0	0	0	0
	2009	0	0	0	0	0	1	1
	2010	0	0	0	0	0	2	2



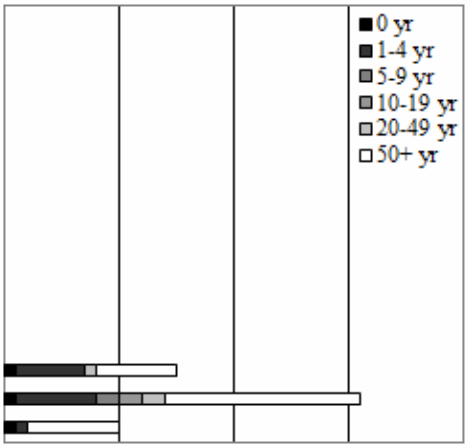
Poliomyelitis **ICD9 045** **ICD10 A80**

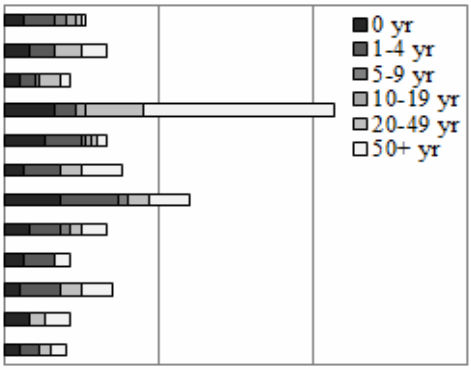
		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Mortality (Acute)	1997	0	0	0	0	0	1	1
	1998	0	0	0	0	0	0	0
	1999	0	0	0	0	0	0	0
	2000	0	0	0	0	0	2	2
	2001	0	0	0	0	1	0	1
	2002	0	0	0	0	0	1	1
	2003	0	0	0	0	0	3	3
	2004	0	0	0	0	0	0	0
	2005	0	0	0	0	0	0	0
	2006	0	0	0	0	0	0	0
	2007	0	0	0	0	0	0	0
	2008	0	0	0	0	0	0	0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

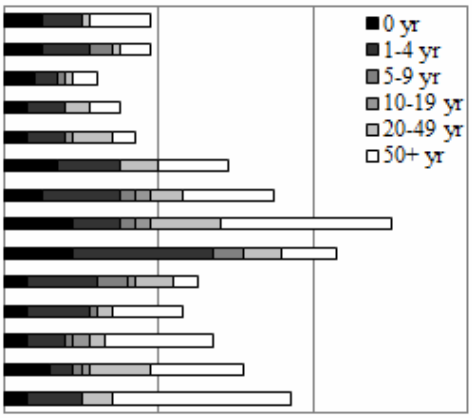


Hib **ICD9 3200** **ICD10 A41.5 G00.0**

		Age (Years) 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	1	7	2	2	2	17	31
	2010	1	1	0	0	0	8	10
Hospitalisation (all types)*	1999	4	6	2	2	1	1	16
	2000	5	5	0	0	5	5	20
	2001	3	3	1	0	4	2	14
	2002	10	4	0	2	11	37	64
	2003	8	7	1	1	1	2	20
	2004	4	7	0	0	4	8	23
	2005	11	11	2	0	4	8	36
	2006	5	6	2	0	2	5	20
	2007	4	6	0	0	0	3	13
	2008	3	8	0	0	4	6	21
	2009	5	0	0	0	3	5	13
	2010	3	4	0	0	2	3	12
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	5	3	17
	2002	7	8	0	0	5	9	29
	2003	5	10	2	2	4	12	35
	2004	9	6	2	2	9	22	50
	2005	9	18	4	0	5	7	43
	2006	3	9	4	1	5	3	25
	2007	3	8	1	0	2	9	23
	2008	3	5	1	2	2	14	27
	2009	6	3	1	1	8	12	31
	2010	3	7	0	0	4	23	37



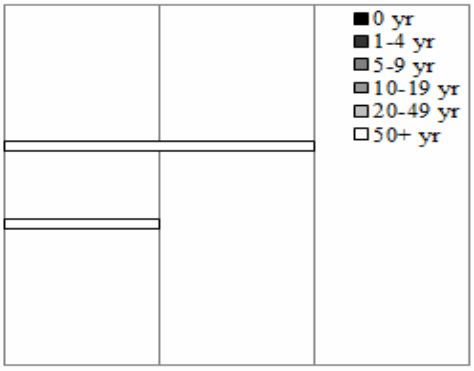


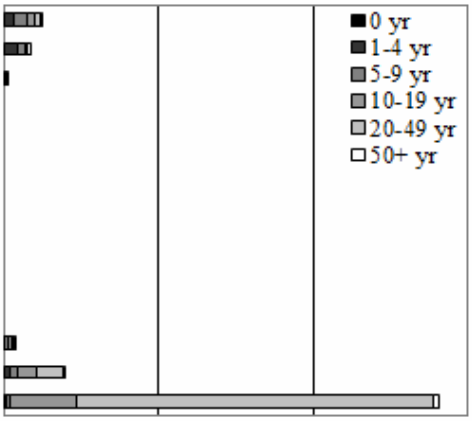


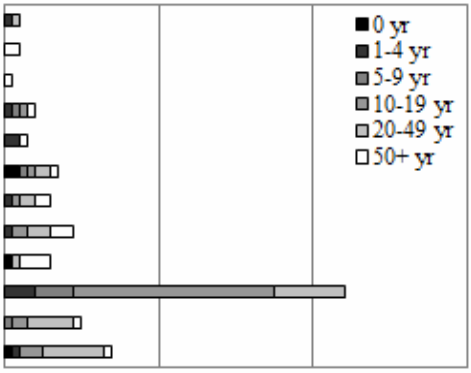
*For some patients the age is unknown.

Mumps **ICD9 072** **ICD10 B26**

		Age (Years) 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	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
	2010	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	9	8	26	33	2	78
	2010	0	3	6	84	463	6	562
Hospitalisation	1999	0	1	0	0	1	0	2
	2000	0	0	0	0	0	2	2
	2001	0	0	0	0	0	1	1
	2002	0	1	1	1	0	1	4
	2003	0	2	0	0	0	1	3
	2004	2	0	1	1	2	1	7
	2005	0	1	0	1	2	2	6
	2006	0	1	0	2	3	3	9
	2007	1	0	0	0	1	4	6
	2008	0	4	5	26	9	0	44
	2009	0	0	1	2	6	1	10
	2010	1	1	0	3	8	1	14

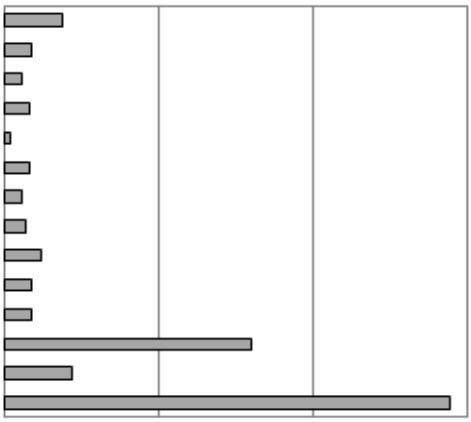






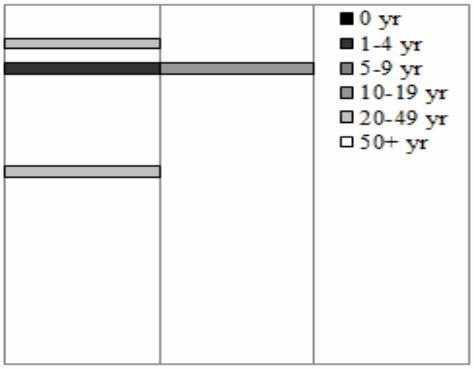
* No notifications between April 1st 1999 – December 31st 2008

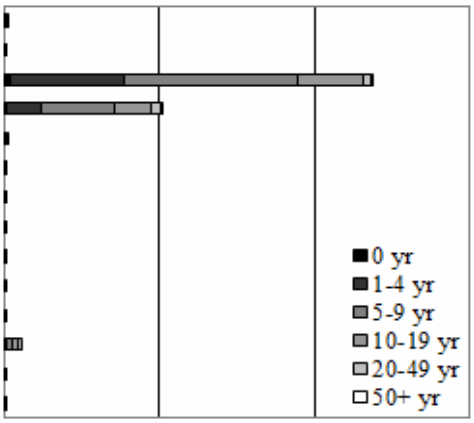
Isolates	Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total	N
1997	-	-	-	-	-	-	19	
1998	-	-	-	-	-	-	9	
1999	-	-	-	-	-	-	6	
2000	-	-	-	-	-	-	8	
2001	-	-	-	-	-	-	2	
2002	-	-	-	-	-	-	8	
2003	-	-	-	-	-	-	6	
2004	-	-	-	-	-	-	7	
2005	-	-	-	-	-	-	12	
2006	-	-	-	-	-	-	9	
2007	-	-	-	-	-	-	9	
2008	-	-	-	-	-	-	80	
2009	-	-	-	-	-	-	22	
2010	-	-	-	-	-	-	144	

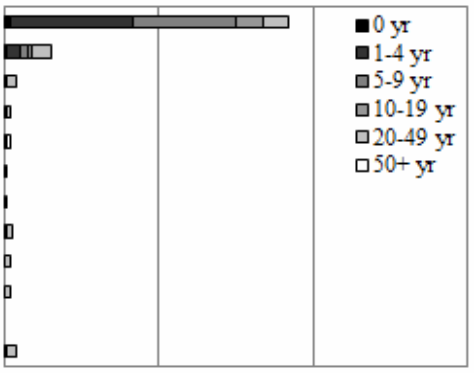


Measles **ICD9 055** **ICD10 B05**

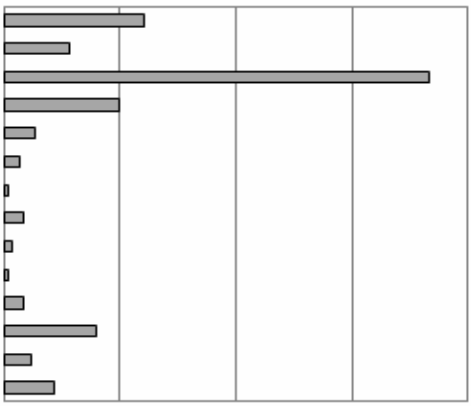
		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Mortality	1997	0	0	0	0	0	0	0
	1998	0	0	0	0	1	0	1
	1999	0	1	0	1	0	0	2
	2000	0	0	0	0	0	0	0
	2001	0	0	0	0	0	0	0
	2002	0	0	0	0	0	0	0
	2003	0	0	0	0	1	0	1
	2004	0	0	0	0	0	0	0
	2005	0	0	0	0	0	0	0
	2006	0	0	0	0	0	0	0
	2007	0	0	0	0	0	0	0
	2008	0	0	0	0	0	0	0
	2009	0	0	0	0	0	0	0
	2010	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	110
	2009	1	2	2	3	7	0	15
	2010	1	2	2	1	9	0	15
Hospitalisation	1999	2	40	33	9	8	0	92
	2000	1	4	3	1	6	0	15
	2001	1	0	0	0	3	0	4
	2002	0	0	0	1	1	0	2
	2003	0	1	0	0	0	1	2
	2004	0	0	0	1	0	0	1
	2005	0	0	0	0	1	0	1
	2006	0	1	0	0	2	0	3
	2007	0	0	0	0	2	0	2
	2008	0	0	0	0	2	0	2
	2009	0	0	0	0	0	0	0
	2010	0	1	0	0	3	0	4





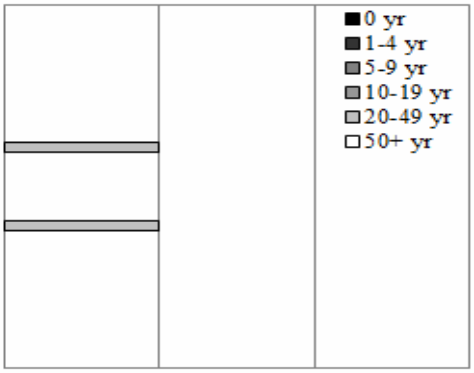


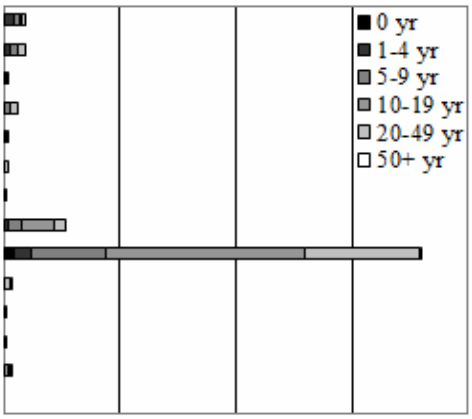
		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total	N
Isolates	1997	-	-	-	-	-	-	36	
	1998	-	-	-	-	-	-	17	
	1999	-	-	-	-	-	-	110	
	2000	-	-	-	-	-	-	30	
	2001	-	-	-	-	-	-	8	
	2002	-	-	-	-	-	-	4	
	2003	-	-	-	-	-	-	1	
	2004	-	-	-	-	-	-	5	
	2005	-	-	-	-	-	-	2	
	2006	-	-	-	-	-	-	1	
	2007	-	-	-	-	-	-	5	
	2008	-	-	-	-	-	-	24	
	2009	-	-	-	-	-	-	7	
	2010	-	-	-	-	-	-	13	

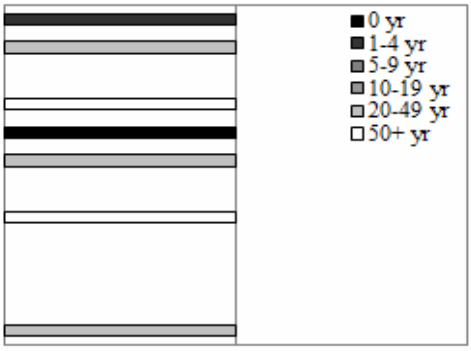


Rubella (Acquired) **ICD9 056** **ICD10 B06**

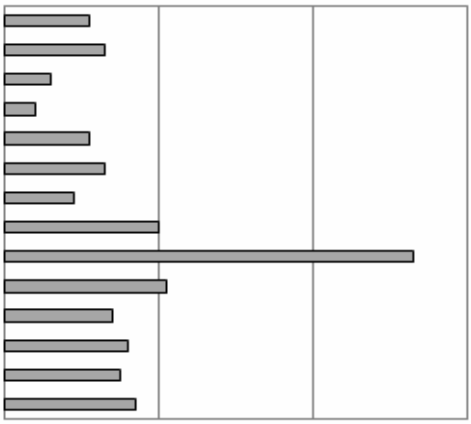
		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Mortality	1997	0	0	0	0	0	0	0
	1998	0	0	0	0	0	0	0
	1999	0	0	0	0	0	0	0
	2000	0	0	0	0	0	0	0
	2001	0	0	0	0	0	0	0
	2002	0	0	0	0	1	0	1
	2003	0	0	0	0	0	0	0
	2004	0	0	0	0	0	0	0
	2005	0	0	0	0	1	0	1
	2006	0	0	0	0	0	0	0
	2007	0	0	0	0	0	0	0
	2008	0	0	0	0	0	0	0
	2009	0	0	0	0	0	0	0
	2010	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	53
	2005	8	15	65	172	98	2	360
	2006	0	1	0	0	4	1	6
	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	0	0	0	0	0	0
Hospitalisation	1999	0	1	0	0	0	0	1
	2000	0	0	0	0	1	0	1
	2001	0	0	0	0	0	0	0
	2002	0	0	0	0	0	1	1
	2003	1	0	0	0	0	0	1
	2004	0	0	0	0	1	0	1
	2005	0	0	0	0	0	0	0
	2006	0	0	0	0	0	1	1
	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	1	0	1





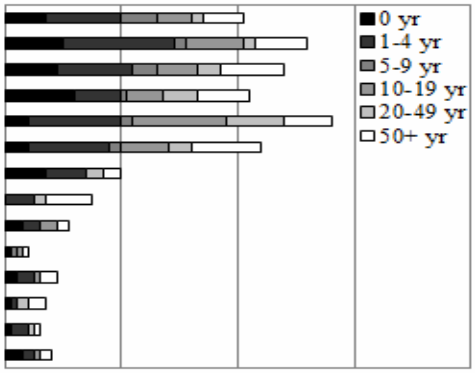


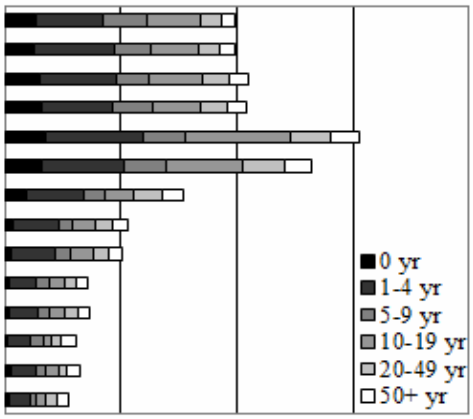
Isolates	Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total	N
1997	-	-	-	-	-	-	11	
1998	-	-	-	-	-	-	13	
1999	-	-	-	-	-	-	6	
2000	-	-	-	-	-	-	4	
2001	-	-	-	-	-	-	11	
2002	-	-	-	-	-	-	13	
2003	-	-	-	-	-	-	9	
2004	-	-	-	-	-	-	20	
2005	-	-	-	-	-	-	53	
2006	-	-	-	-	-	-	21	
2007	-	-	-	-	-	-	14	
2008	-	-	-	-	-	-	16	
2009	-	-	-	-	-	-	15	
2010	-	-	-	-	-	-	17	

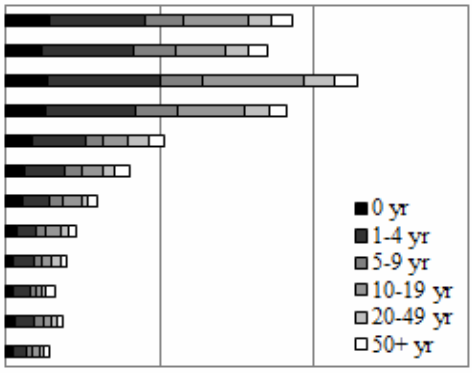


Meningococcal disease **ICD9 036.0-4, 036.8-9** **ICD10 A39**

		Age (Years) 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
	2010	3	2	0	1	0	2	8
Notifications*	1997	66	146	93	118	44	28	495
	1998	65	169	79	105	44	35	501
	1999	76	164	69	117	56	42	524
	2000	80	153	84	104	58	42	521
	2001	87	212	91	224	86	63	766
	2002	80	175	92	166	90	56	661
	2003	45	127	42	65	60	46	386
	2004	17	99	31	47	36	36	266
	2005	14	95	33	48	33	29	252
	2006	11	56	28	33	25	27	180
	2007	8	64	25	32	29	23	181
	2008	6	48	29	19	17	36	155
	2009	14	54	20	28	16	28	160
	2010	9	47	12	21	22	28	139
Hospitalisation (036.0, 036.2-3)*	1999	113	251	97	167	62	52	745
	2000	97	234	110	129	61	48	682
	2001	112	291	109	261	77	59	917
	2002	106	233	108	174	65	41	742
	2003	71	138	44	63	56	41	416
	2004	52	102	46	55	28	41	325
	2005	45	70	37	45	17	24	240
	2006	31	48	26	40	19	19	185
	2007	23	55	19	22	24	15	158
	2008	20	46	15	13	10	28	132
	2009	27	47	24	24	14	12	149
	2010	20	38	12	18	11	18	118





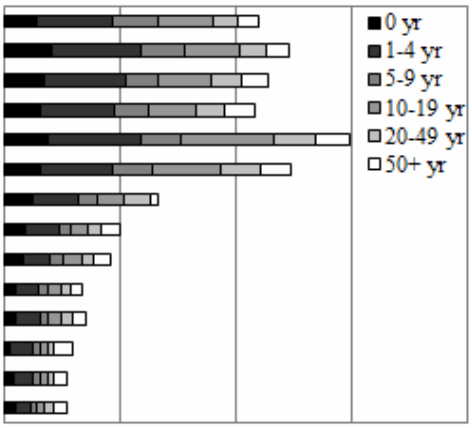


*For some patients the age is unknown.

	Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
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	97	199	84	203	89	73	745
2002	78	158	84	146	88	66	621
2003	63	99	39	56	58	16	362
2004	44	76	22	40	28	42	252
2005	40	59	29	42	25	36	231
2006	25	49	21	27	22	25	169
2007	27	51	17	29	25	27	176
2008	15	46	16	16	16	39	148
2009	22	41	15	16	15	26	138
2010	24	33	12	17	22	28	136

Isolates*

N

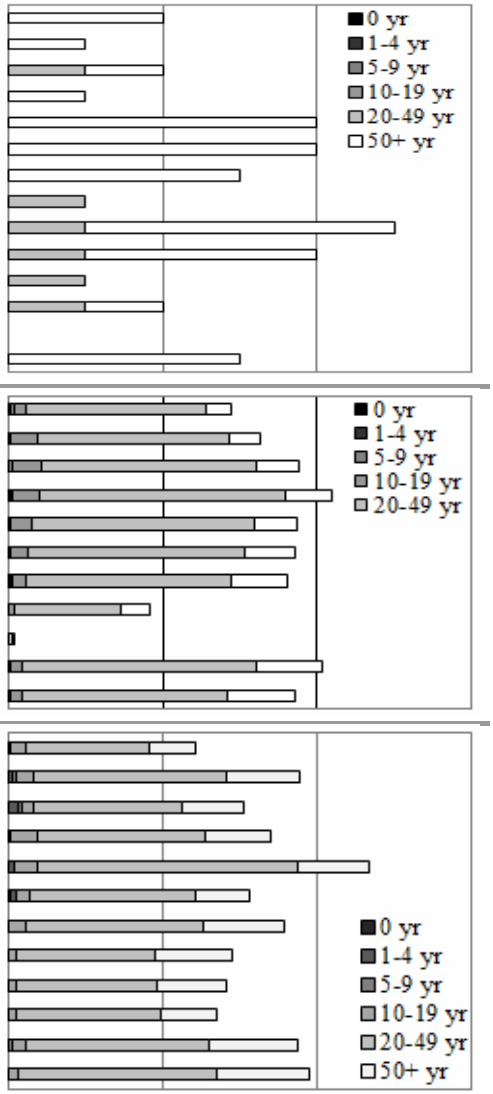


*For some patients the age is unknown.

Hepatitis B **ICD9 070.2-3 ICD10 B16 B17.0 B18.0 B18.1**

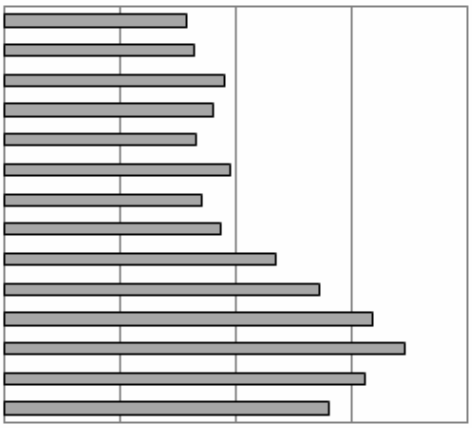
		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Mortality (B16; Acute)	1997	0	0	0	0	0	2	2
	1998	0	0	0	0	0	1	1
	1999	0	0	0	0	1	1	2
	2000	0	0	0	0	0	1	1
	2001	0	0	0	0	0	4	4
	2002	0	0	0	0	0	4	4
	2003	0	0	0	0	0	3	3
	2004	0	0	0	0	1	0	1
	2005	0	0	0	0	1	4	5
	2006	0	0	0	0	1	3	4
	2007	0	0	0	0	1	0	1
	2008	0	0	0	0	1	1	2
	2009	0	0	0	0	0	0	0
	2010	0	0	0	0	0	3	3
Notifications	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	32
	2009	0	7	5	81	1519	424	2036
	2010	0	8	11	68	1330	441	1858
Hospitalisations*	1999	0	0	2	9	80	30	121
	2000	1	2	2	11	125	48	193
	2001	0	7	2	8	95	40	156
	2002	1	0	1	17	108	43	173
	2003	0	4	0	15	168	46	235
	2004	2	4	0	8	107	35	160
	2005	0	0	0	11	115	53	180
	2006	0	0	0	6	89	50	147
	2007	0	1	0	5	90	45	142
	2008	0	1	0	5	93	36	136
	2009	0	1	2	8	119	57	188
	2010	0	0	0	7	128	60	197

N



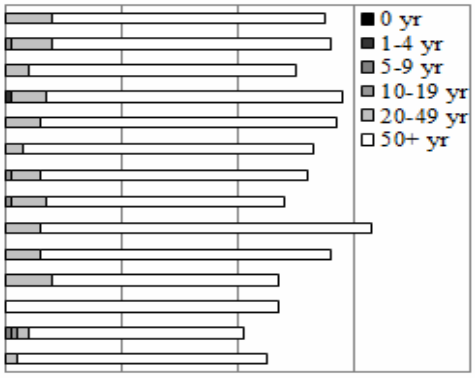
*For some patients the age is unknown.

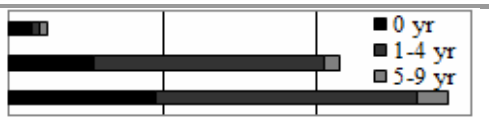
	Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total	N
Isolates 1997	-	-	-	-	-	-	787	
1998	-	-	-	-	-	-	819	
1999	-	-	-	-	-	-	950	
2000	-	-	-	-	-	-	904	
2001	-	-	-	-	-	-	827	
2002	-	-	-	-	-	-	974	
2003	-	-	-	-	-	-	849	
2004	-	-	-	-	-	-	932	
2005	-	-	-	-	-	-	1174	
2006	-	-	-	-	-	-	1361	
2007	-	-	-	-	-	-	1588	
2008	-	-	-	-	-	-	1725	
2009	-	-	-	-	-	-	1553	
2010	-	-	-	-	-	-	1401	

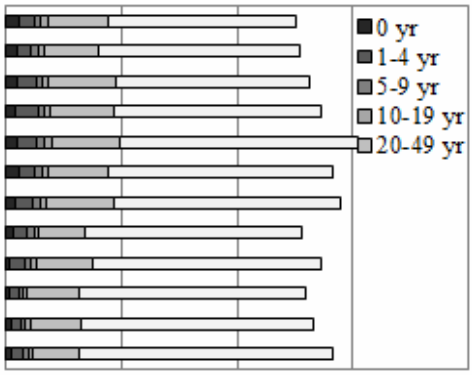


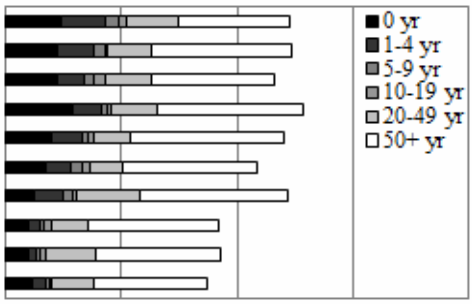
Pneumococcal disease **ICD9 0382, 481, 4823, 3201** **ICD10 J13, 18.0, 18.9, G00.1, A40.4**

		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Mortality (J13; Pneumonia)	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	53
	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
	2010	0	0	0	0	2	43	45
Notifications	2008	3	1	1*	-	-	-	5
	2009	10	31	2*	-	-	-	43
	2010	19	34	4*	-	-	-	57
Hospitalisations**	1999	124	126	63	52	529	1622	2521
	2000	113	110	60	53	476	1727	2544
	2001	108	170	53	48	576	1676	2638
	2002	97	188	61	42	544	1796	2734
	2003	109	171	56	71	587	2047	3057
	2004	120	144	66	44	523	1930	2832
	2005	94	146	68	51	580	1951	2899
	2006	76	116	56	45	400	1860	2557
	2007	42	124	53	48	488	1963	2727
	2008	34	92	35	31	451	1941	2590
	2009	54	79	38	47	435	2012	2672
	2010	64	85	50	43	390	2200	2839
Isolates**	2001	48	39	11	7	45	95	245
	2002	46	31	9	2	38	121	247
	2003	46	23	8	10	39	107	233
	2004	58	25	6	3	39	126	257
	2005	41	25	6	4	32	132	240
	2006	35	22	9	8	27	116	217
	2007	26	24	8	4	55	126	244
	2008	20	10	3	8	30	114	185
	2009	20	7	4	4	43	108	186
	2010	24	11	4	2	36	98	175









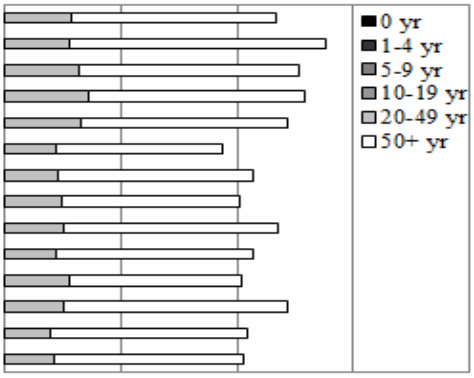
*Notifiable for 0- to 5-year-old children

**For some patients the age is unknown.

HPV **ICD9 -** **ICD10 C53**

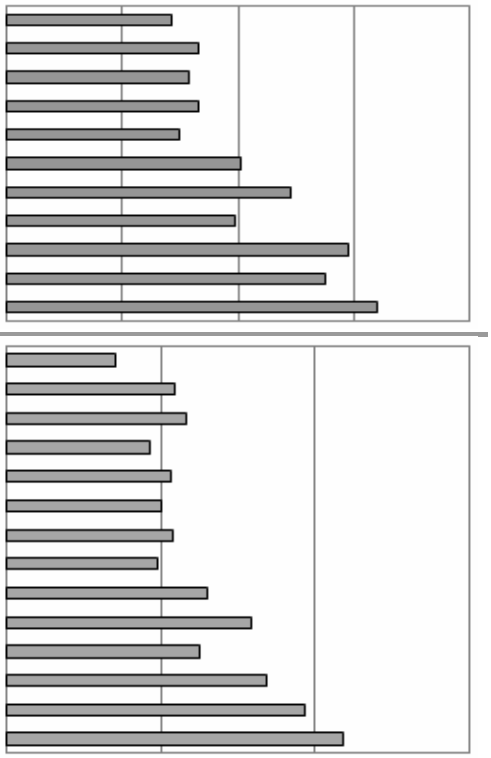
	Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Mortality (Cervical cancer) 1997	0	0	0	0	58	176	234
1998	0	0	0	1	56	219	276
1999	0	0	0	0	64	189	253
2000	0	0	0	0	73	185	258
2001	0	0	0	0	66	177	243
2002	0	0	0	0	45	142	187
2003	0	0	0	0	47	167	214
2004	0	0	0	0	49	154	203
2005	0	0	0	0	52	183	235
2006	0	0	0	0	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
2010	0	0	0	0	43	162	205

N



Rotavirus **ICD9 -** **ICD10 -**

		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Hospitalisations (estimation)	2000	-	-	-	-	-	-	2864
	2001	-	-	-	-	-	-	3312
	2002	-	-	-	-	-	-	3160
	2003	-	-	-	-	-	-	3322
	2004	-	-	-	-	-	-	3000
	2005	-	-	-	-	-	-	4063
	2006	-	-	-	-	-	-	4903
	2007	-	-	-	-	-	-	3948
	2008	-	-	-	-	-	-	5895
	2009	-	-	-	-	-	-	5501
	2010	-	-	-	-	-	-	6392
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	-	-	-	-	-	-	2180



Varicella (Chickenpox) **ICD9 052** **ICD10 B01**

		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Mortality	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
	2010	0	0	0	0	0	2	2
Hospitalisations	2000	44	95	14	6	38	14	211
	2001	62	104	19	3	36	9	233
	2002	47	113	17	4	29	9	219
	2003	78	121	10	6	41	17	273
	2004	89	115	20	7	26	12	269
	2005	64	119	9	1	28	17	238
	2006	108	132	17	4	33	19	313
	2007	69	92	19	4	24	23	231
	2008	74	111	19	3	38	26	271
	2009	67	92	18	6	37	22	242
	2010	81	136	21	7	39	31	315

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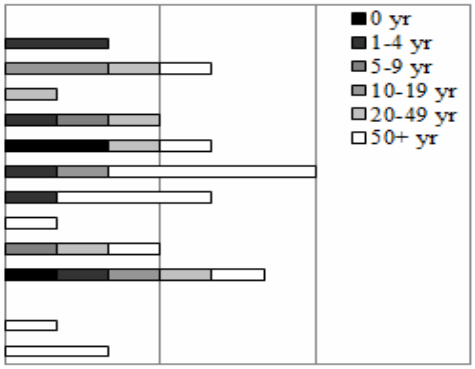
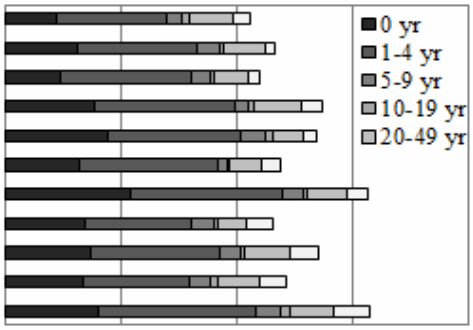
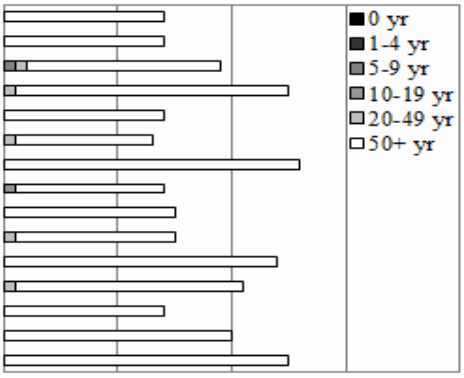
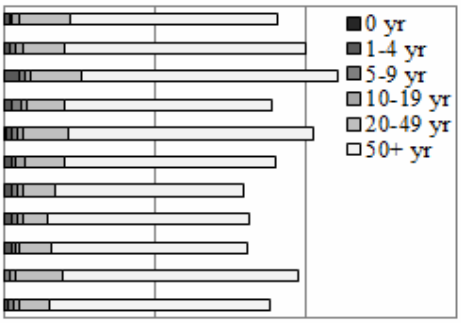




Herpes zoster (Shingles) **ICD9 053** **ICD10 B02**

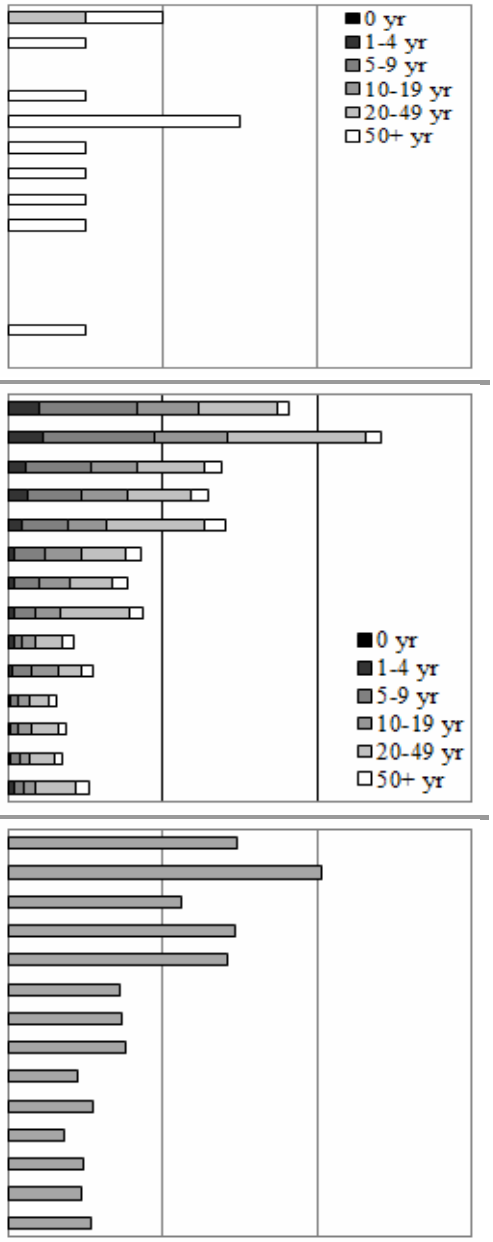
		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Mortality	1997	0	0	0	0	0	14	14
	1998	0	0	1	0	1	17	19
	1999	0	0	0	0	1	24	25
	2000	0	0	0	0	0	14	14
	2001	0	0	0	0	1	12	13
	2002	0	0	0	0	0	26	26
	2003	0	0	0	1	0	13	14
	2004	0	0	0	0	0	15	15
	2005	0	0	0	0	1	14	15
	2006	0	0	0	0	0	24	24
	2007	0	0	0	0	1	20	21
	2008	0	0	0	0	0	14	14
	2009	0	0	0	0	0	20	20
	2010	0	0	0	0	0	25	25
Hospitalisations	2000	2	6	4	9	68	274	363
	2001	1	8	7	9	55	319	399
	2002	2	18	7	8	67	340	442
	2003	1	9	14	6	51	273	354
	2004	4	8	6	7	60	324	409
	2005	2	9	5	11	54	278	359
	2006	0	11	7	7	43	249	317
	2007	1	10	7	8	33	267	326
	2008	2	8	5	6	43	259	323
	2009	0	2	6	7	63	311	389
	2010	1	6	6	8	39	292	352





Hepatitis A **ICD9 -** **ICD10 B15**

		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Mortality (Acute)	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
	2010	0	0	0	0	0	0	0
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	189
	2009	0	8	34	28	83	23	176
	2010	0	18	32	41	127	44	262
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	-	-	-	-	-	-	107



Appendix 3 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 1st 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: MenC added at 14 months of age, for all children born on or after 1st 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	**MenC**	**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 1st 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	MenC	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 1st 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	MenC	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 1st 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	MenC	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	MenC	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	MenC	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 Priorix/GSK MMR VaxPro/SP MSD**	MenC	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 Priorix/GSK MMR VaxPro/SP MSD**	MenC	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 1st 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; and for the risk groups HBVAXPRO/SP has been replaced by Engerix-B Junior.)

In general

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
0-1 year*	DTaP-IPV/Hib	**Pediacel/SP MSD** **Infanrix IPV+Hib/GSK**	Pneumo	Prevenar/Wyeth
14 months	MMR	**MMR vaccine/NVI Priorix/GSK** **MMR VaxPro/SP MSD**	MenC	NeisVac-C/Baxter
4 years	DTaP -IPV	Triaxis Polio/SP MSD* **Infanrix IPV/GSK**		
9 years	DT-IPV	DT-IPV vaccine/NVI	MMR	**MMR vaccine/ NVI 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*	**Engerix-B Junior/GSK**		
0-1 year**	DTaP-HBV-IPV/Hib***	Infanrix hexa/GSK	Pneumo	Prevenar/Wyeth
14 months	MMR	**MMR vaccine/NVI Priorix/GSK** **MMR VaxPro/SP MSD**	MenC	NeisVac-C/Baxter
4 years	DTaP-IPV	Triaxis Polio/SP MSD**** **Infanrix IPV/GSK**		
9 years	DT-IPV	DT-IPV vaccine/NVI	MMR	**MMR vaccine/ NVI 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
**** 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 Infanrix IPV+Hib/GSK	Pneumo	Prevenar/Wyeth
14 months	MMR	Priorix/GSK MMR VaxPro/SP MSD**	MenC	NeisVac-C/Baxter
4 years	DTaP -IPV	Infanrix IPV/GSK		
9 years	DT-IPV	DT-IPV vaccine/NVI	MMR	Priorix/GSK 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*	Engerix-B Junior/GSK		
0-1 year**	DTaP-HBV-IPV/Hib***	Infanrix hexa/GSK	Pneumo	Prevenar/Wyeth
14 months	MMR	Priorix/GSK MMR VaxPro/SP MSD****	MenC	NeisVac-C/Baxter
4 years	DTaP-IPV	Infanrix IPV/GSK		
9 years	DT-IPV	DT-IPV vaccine/NVI	MMR	Priorix/GSK MMR VaxPro/ 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
**** in 2009 only MMRVaxPro is administered

Table A10 NIP from 1st January 2010 – 1st March 2011
(change: in 2010 vaccination against human papilloma virus infection was introduced for 12-year-old girls. This introduction was preceded in 2009 by a catch-up vaccination campaign for girls born in 1993-1996; as from 2010, Infanrix IPV+Hib/GSK was not used anymore.)

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 VaxPro/SP MSD	MenC	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 intervals

Specified risk groups

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
At birth	HBV*	Engerix-B Junior/GSK		
0-1 year**	DTaP-HBV-IPV/Hib***	Infanrix hexa/GSK	Pneumo	Prevenar/Wyeth
14 months	MMR	MMR VaxPro/SP MSD	MenC	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
**** only girls were vaccinated and received 3 doses HPV vaccine at 0,1 and 6 months intervals

Table A11 NIP from 1st March 2011 – 1st August 2011
(change: the pneumococcal vaccine Prevenar/Wyeth is replaced by Synflorix/GSK for children born on or after 1st March 2011.)

In general

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
0-1 year*	DTaP-IPV/Hib	Pediacel/SP MSD	Pneumo	**Synflorix/GSK**
14 months	MMR	MMR VaxPro/SP MSD	MenC	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 intervals

Specified risk groups

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
At birth	HBV*	Engerix-B Junior/GSK		
0-1 year**	DTaP-HBV-IPV/Hib***	Infanrix hexa/GSK	Pneumo	**Synflorix/GSK**
14 months	MMR	MMR VaxPro/SP MSD	MenC	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
**** only girls were vaccinated and received 3 doses HPV vaccine at 0,1 and 6 months intervals

Table A12 NIP from 1st August 2011 onwards
(change: hepatitis B vaccination for all children born on or after 1st August 2011 is included in the NIP, Infanrix IPV+Hib/GSK was replaced by Infanrix hexa/GSK.)

In general

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
0-1 year*	**DTaP-HBV-IPV/Hib**	Pediacel/SP MSD **Infanrix hexa/GSK**	Pneumo	Synflorix/GSK
14 months	MMR	MMR VaxPro/SP MSD	MenC	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 intervals

Specified risk groups

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
At birth	HBV*	Engerix-B Junior/GSK		
0-1 year**	DTaP-HBV-IPV/Hib	Infanrix hexa/GSK	Pneumo	Synflorix/GSK
14 months	MMR	MMR VaxPro/SP MSD	MenC	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 girls were vaccinated and received 3 doses HPV vaccine at 0,1 and 6 months intervals

Appendix 4 Composition of vaccines used in 2011

Vaccine	Composition
Pediacel/SP MSD	Purified diphtheria toxoid > 30 IU
RVG 32118	Purified tetanus toxoid > 40 IU
Diphtheria, tetanus, 5 component acellular pertussis vaccine, inactivated poliomyelitis vaccine	Purified pertussis toxoid (PT) 20 µg
	Purified filamentous haemagglutinin (FHA) 20 µg
	Purified fimbrial agglutinogens 2 and 3 (FIM) 5 µg
and conjugated *Haemophilus influenzae* type b-vaccin (adsorbed)	Purified pertactin (PRN) 3 µg
	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
	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) and inactivated poliomyelitis vaccine	Inactivated poliovirus type 1 > 40 DU
	Inactivated poliovirus type 2 > 4 DU
	Inactivated poliovirus type 3 > 7.5 DU
1 ml	*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 vaccine (adsorbed)	Pneumococcal polysaccharide serotype 9V* 2 µg
	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 adsorbed to aluminium phosphate 0.5 mg
Synfloris/GSK	Pneumococcal polysaccharide serotype $1^{1,2}$ 1 µg
	Pneumococcal polysaccharide serotype $4^{1,2}$ 3 µg
	Pneumococcal polysaccharide serotype $5^{1,2}$ 1 µg
	Pneumococcal polysaccharide serotype $6B^{1,2}$ 1 µg
	Pneumococcal polysaccharide serotype $7F^{1,2}$ 1 µg
	Pneumococcal polysaccharide serotype $9V^{1,2}$ 1 µg
	Pneumococcal polysaccharide serotype $14^{1,2}$ 1 µg
	Pneumococcal polysaccharide serotype $18C^{1,3}$ 3 µg
	Pneumococcal polysaccharide serotype $19F^{1,4}$ 3 µg
	Pneumococcal polysaccharide serotype $23F^{1,2}$ 1 µg
	[1]Absorbed to aluminium phosphate 0.5 mg Al3+
	[2]Conjugated to protein D (obtained from non-typable *Haemophilus influenzae*) carrier protein 9-16 mg
	[3]Conjugated to tetanus toxoid 5-10 mg
	[3]Conjugated to diphtheria toxoid 3-6 mg
NeisVac-C/Baxter	Neisseria meningitidis (C11-strain)
RVG 26343	Polysaccharide O-deacetylated 10 µg
Conjugated meningococcal C saccharide vaccine (adsorbed)	Conjugated to tetanus toxoid 10-20 µg
	adsorbed to aluminium hydroxide 0.5 mg Al^{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 component), hepatitis B (rDNA), inactivated poliomyelitis vaccine and conjugated *Haemophilus influenzae* type b-vaccine (adsorbed)	Adsorbed pertussis toxoid (PT) 25 µg Adsorbed filamentous haemagglutinin (FHA) 25 µg Adsorbed pertactin (PRN) 8 µg Adsorbed recombinant HBsAg protein 10 µg 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 (PRP) 10 µg covalently bound to tetanus toxoid (T) 20-40 µg
MMR Vax /SP MSD	Mumps virus (Jeryl Lynn) > 5000 TCID50 (tissue culture infectious doses)
RVG 17672	Measles virus (Schwartz) > 1000 TCID50
Mumps, measles and rubella vaccine	Rubella virus (Wistar RA 27/3) > 1000 TCID50
0.5 ml	
Infanrix IPV + Hib / GSK	Adsorbed diphtheria toxoid > 30 IU
RVG 22123 / RVG 34567	Adsorbed tetanus toxoid 20 - 40 IU
Diphtheria, tetanus, pertussis (acellular component), inactivated poliomyelitis vaccine and conjugated *Haemophilus influenzae* type b-vaccine (adsorbed)	Adsorbed pertussis toxoid (PT) 25 µg Adsorbed filamentous haemagglutinin (FHA) 25 µg Absorbed pertactin (PRN) 8 µg 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 *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 (acellular component), inactivated poliomyelitis vaccine	Adsorbed pertussis toxoid (PT) 25 µg Adsorbed filamentous haemagglutinin (FHA) 25 µg 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 culture infectious doses)
EU/1/06/337/001	Measles virus (Enders' Edmonston) > 1000 TCID50
Mumps, measles and rubella vaccine	Rubella virus (Wistar RA 27/3) > 1000 TCID50
0.5 ml	
Engerix-B Junior	Hepatitis B-virus surface antigen, recombinant* (S protein) absorbed 10 µg *produced on genetically-engineering yeast cells (Saccharomyces cerevisiae)
Cervarix / GSK	Human papillomavirus type 16 L1 protein[2,3,4] 20 µg Human papillomavirus type 18 L1 protein[2,3,4] 20 µg [1]Adjuvanted by AS04 containing 3-O-desacyl-4'-monophosphoryl lipid A (MPL)[3] 50 µg [2]Absorbed on aluminium hydroxide, hydrated ($Al(OH)_3$) 0.5 mg AL^{3+} in total [3]L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system which uses Hi-5 Rix4446 cells derived from *Trichoplusia ni.*

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