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

The National Immunisation Programme in the Netherlands

Developments in 2012

RIVM report 201001002/2012

T.M. van 't Klooster et al.

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

The National Immunisation Programme in the Netherlands

Developments in 2012

RIVM Report 201001002/2012

Colophon

Editors:
T.M. van 't Klooster
H.E. de Melker

Report prepared by:
H.G.A.M. van der Avoort[1], W.A.M. Bakker[1], G.A.M. Berbers[1], R.S. van Binnendijk[1], M.C. van Blankers[1], J.A. Bogaards[1], H.J. Boot[1†], M.A.C. de Bruijn[1], P. Bruijning-Verhagen[1], A. Buisman[1], C.A.C.M. van Els[1], A. van der Ende[4], I.H.M. Friesema[1], S.J.M. Hahné[1], C.W.G. Hoitink[1], P. Jochemsen[1], P. Kaaijk[1], J.M. Kemmeren[1], A.J. King[1], F.R.M. van der Klis[1], T.M. van 't Klooster[1], M.J. Knol[1], F. Koedijk[1], A. Kroneman[1], E.A. van Lier[1], A.K. Lugner[1], W. Luytjes[1], N.A.T. van der Maas[1], L. Mollema[1], M. Mollers[1], F.R. Mooi[1], S.H. Mooij[5], D.W. Notermans[1], W. van Pelt[1], F. Reubsaet[1], N.Y. Rots[1], M. Scherpenisse[1], I. Stirbu-Wagner[3], A.W.M. Suijkerbuijk[2], L.P.B. Verhoef[1], H.J. Vriend[1]

[1] Centre for Infectious Disease Control, RIVM
[2] Centre for Prevention and Health Services Research, RIVM
[3] Netherlands Institute for Health Services Research, NIVEL
[4] Reference Laboratory for Bacterial Meningitis, AMC
[5] Public Health Service Amsterdam

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

This investigation has been performed by order and for the account of Ministry of Health, Welfare and Sports, within the framework of V201001, Development future National Immunisation Programme.

Abstract

The National Immunisation Programme in the Netherlands
Developments in 2012

The National Institute for Public Health and the Environment (RIVM) annually presents developments in the National Immunisation Programme (NIP). It gives an overview of how often diseases included in the NIP do occur and the changes made in the programme. The report also indicates which vaccines are used and which side effects were reported after vaccination. Developments for potential target diseases are included as well. The participation level in the NIP has been high for many years, resulting in low incidences for most target diseases. The programme is also safe because there are relative few side effects, which are usually mild and transient. For an optimal programme, continuous monitoring stays necessary.

Notable developments in 2011 and 2012
In 2011, the vaccine against pneumococcal disease was extended with three types. It is still too early to see an effect. The number of notifications of acute hepatitis B infections dropped to an all time low since hepatitis B could first be diagnosed (late 1960s). In 2011 the NIP incorpored hepatitis B vaccination for all infants in order to prevent the disease furthermore.

Despite the introduction of more effective vaccines and an additional booster at 4 years of age, a large pertussis epidemic occurred in 2012 in the Netherlands. The increase was the highest in infants of 0-2 months of age, children 8 years and older and adults. The increase from 8-years of age can be partly explained by a decreasing vaccine effectiveness as from this age.

The mumps outbreak that started late 2009 among students continued up to 2012. Nevertheless, the number of reported cases in the season 2011/2012 was lower than in the previous season.
In 2011, 50 cases of measles were reported. The incidence of non-imported cases (34 cases) was above the WHO elimination target (one per million inhabitants).

In 2011, the vaccination against cervical cancer (HPV) for the first group of 12-year-olds was completed. Of them 56 percent was fully vaccinated (three doses).

Potential new target diseases
With regard to potential new target diseases, the incidence of meningococcal serogroup B disease has further decreased in 2011, although the incidence of meningococcal serogroup Y has increased in 2011. The rise in incidence of rotavirus-associated gastroenteritis did not continue in 2011. The number of hepatitis A infections was the lowest since this became notifiable in 1999. For varicella and herpes zoster, no striking changes occurred in 2011.

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

Rapport in het kort

Het Rijksvaccinatieprogramma in Nederland
Ontwikkelingen in 2012

Het RIVM geeft jaarlijks een overzicht hoe vaak ziekten uit het Rijksvaccinatieprogramma (RVP) voorkomen en welke veranderingen daarin plaatsvinden. Het overzicht geeft ook aan welke vaccins zijn gebruikt en welke bijwerkingen na vaccinaties optraden. Hetzelfde geldt voor ontwikkelingen over nieuwe vaccins die eventueel in de toekomst in het RVP worden opgenomen. De vaccinatiegraad is al vele jaren hoog, waardoor weinig mensen ziekten krijgen waartegen zij via het RVP worden gevaccineerd. Het vaccinatieprogramma is bovendien veilig omdat er relatief weinig bijwerkingen voorkomen, die doorgaans niet ernstig van aard zijn. Voor een optimaal programma blijft continue monitoring nodig.

Opvallende ontwikkelingen in 2011 en 2012
In 2011 is het vaccin tegen pneumokokkenziekte uitgebreid met drie typen van deze bacterie. Het is nog te vroeg om daar effect van te zien. Het aantal meldingen van acute hepatits B-infecties is nog nooit zo laag geweest sinds de ontdekking van het virus eind jaren zestig van de vorige eeuw. Met de invoering van het hepatitis B-vaccin in 2011 voor alle zuigelingen (voorheen was dat een beperktere doelgroep) hoopt het RVP nog meer hepatitis B te voorkomen.

In 2012 deed zich in Nederland een kinkhoestepidemie voor, hoewel het vaccin in 2005 is verbeterd en een extra booster op 4-jarige leeftijd aan het vaccinatieschema is toegevoegd. De ziekte kwam het meest voor bij baby's tussen 0 en 2 maanden oud, kinderen van 8 jaar en ouder, en volwassenen. De toename vanaf 8-jarige leeftijd is onder andere te verklaren doordat het vaccin vanaf die leeftijd minder effectief wordt.

De bofuitbraak die begon in 2009 onder doorgaans gevaccineerde studenten, hield aan tot in 2012. Wel was het aantal meldingen lager dan in 2011 en 2010. In totaal zijn er 50 gevallen van mazelen gemeld in 2011. Het aantal niet-geïmporteerde gevallen (34 gevallen) was hoger dan de doelstelling die de WHO daarvoor heeft opgesteld (één per miljoen inwoners).

In 2011 waren de inentingen tegen baarmoederhalskanker (HPV) voor de eerste groep 12-jarigen afgerond. Van hen had 56 procent zich volledig laten inenten (3 doses).

Mogelijke toevoegingen aan RVP
Van de ziekten die in de toekomst mogelijk onder het RVP gaan vallen, kwam meningokokken B in 2011 steeds minder vaak voor, maar meningokokken Y juist vaker. Maagdarminfecties veroorzaakt door het rotavirus namen niet verder toe. Het aantal hepatitis A-gevallen was in 2011 het laagst sinds de ziekte in 1999 meldingsplichtig is geworden. Voor waterpokken en gordelroos zijn geen grote veranderingen waargenomen.

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

Preface

This report presents an overview of the developments in 2012 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 infection (VZV) 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 includes also other meningococcal serogroups (i.e. non-serogroup B and C types) to enable study of the trends in these serogroups. In addition, data on vaccines for infectious diseases tested in clinical trials which are relevant for the Netherlands, are included in this report.

The report is structured as follows: Chapter 1 gives a short introduction, while in Chapter 2 surveillance methods 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). If applicable, recent and planned changes in NIP are mentioned. Results of ongoing studies are described, together with the planning of future studies and international developments. Chapter 5 describes new target diseases which might need consideration for the future NIP. Finally, in Chapter 6 vaccines for infectious diseases, which 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.

Contents

Summary—13

1 Introduction—17

2 Surveillance methodology—19
2.1 Disease surveillance—19
2.1.1 Mortality data—19
2.1.2 Morbidity data—19
2.1.3 Laboratory data—20
2.2 Molecular surveillance of the pathogen—21
2.3 Immunosurveillance—21
2.4 Vaccination coverage—21
2.5 Surveillance of adverse events following vaccination—21
2.6 Vaccine effectiveness—22

3 Vaccination coverage—23
3.1 Acceptance of vaccination—24

4 Current National Immunisation Programme—27
4.1 Diphtheria—27
4.1.1 Key points—27
4.1.2 Changes in vaccine 2011-2012-2013—27
4.1.3 Epidemiology—27
4.1.4 Pathogen—27
4.1.5 Adverse events—27
4.1.6 Current/ongoing research—27
4.1.7 International developments—27
4.2 Pertussis—28
4.2.1 Key points—28
4.2.2 Changes in vaccine 2011-2012-2013—28
4.2.3 Epidemiology—28
4.2.4 Pathogen—32
4.2.5 Adverse events—33
4.2.6 Current/ongoing research—33
4.2.7 International developments—34
4.3 Tetanus—35
4.3.1 Key points—35
4.3.2 Changes in vaccine 2011-2012-2013—35
4.3.3 Epidemiology—35
4.3.4 Pathogen—36
4.3.5 Adverse events—36
4.3.6 Current/ongoing research—36
4.3.7 International developments—36
4.4 Poliomyelitis—37
4.4.1 Key points—37
4.4.2 Changes in vaccine 2011-2012-2013—37
4.4.3 Epidemiology—37
4.4.4 Pathogen—39
4.4.5 Adverse events—40
4.4.6 Current/ongoing research—41
4.4.7 International developments—41

4.5 *Haemophilus influenzae* serotype b (Hib) disease—42
4.5.1 Key points—42
4.5.2 Changes in vaccine 2011-2012-2013—42
4.5.3 Epidemiology—42
4.5.4 Pathogen—44
4.5.5 Adverse events—44
4.5.6 Current/ongoing research—44
4.5.7 International developments—44
4.6 Mumps—45
4.6.1 Key points—45
4.6.2 Changes in vaccine 2011-2012-2013—45
4.6.3 Epidemiology—45
4.6.4 Pathogen—47
4.6.5 Adverse events—47
4.6.6 Current/ongoing research—47
4.6.7 International developments—48
4.7 Measles—48
4.7.1 Key points—48
4.7.2 Changes in vaccine 2011-2012-2013—48
4.7.3 Epidemiology—48
4.7.4 Pathogen—49
4.7.5 Adverse events—49
4.7.6 Current/ongoing research—49
4.7.7 International developments—50
4.8 Rubella—50
4.8.1 Key points—50
4.8.2 Changes in vaccine 2011-2012-2013—50
4.8.3 Epidemiology—50
4.8.4 Pathogen—51
4.8.5 Adverse events—51
4.8.6 Current/ongoing research—51
4.8.7 International developments—51
4.9 Meningococcal serogroup C disease—51
4.9.1 Key points—51
4.9.2 Changes in vaccine 2011-2012-2013—51
4.9.3 Epidemiology—51
4.9.4 Pathogen—52
4.9.5 Adverse events—52
4.9.6 Current/ongoing research—53
4.9.7 International developments—53
4.10 Hepatitis B—53
4.10.1 Key points—53
4.10.2 Changes in vaccine 2011-2012-2013—54
4.10.3 Epidemiology—54
4.10.4 Pathogen—55
4.10.5 Adverse events—56
4.10.6 Current/ongoing research—56
4.10.7 International developments—56
4.11 Pneumococcal disease—57
4.11.1 Key points—57
4.11.2 Changes in vaccine 2011-2012-2013—57
4.11.3 Epidemiology—57
4.11.4 Pathogen—60
4.11.5 Adverse events—60
4.11.6 Current/ongoing research—60

4.11.7 International developments—62
4.12 Human papillomavirus (HPV) infection—63
4.12.1 Key points—63
4.12.2 Changes in 2011-2012-2013—63
4.12.3 Epidemiology—63
4.12.4 Adverse events—64
4.12.5 Current/Ongoing research—65
4.12.6 Other relevant (international) developments—69

5 Future NIP candidates—71
5.1 Rotavirus infection—71
5.1.1 Key points—71
5.1.2 Epidemiology—71
5.1.3 Pathogen—71
5.1.4 Adverse events—71
5.1.5 Current/ongoing research—72
5.1.6 International developments—72
5.2 Varicella zoster virus (VZV) infection—74
5.2.1 Key points—74
5.2.2 Epidemiology—74
5.2.3 Pathogen—78
5.2.4 Adverse events—79
5.2.5 Current/ongoing research—80
5.2.6 International developments—82
5.3 Hepatitis A—83
5.3.1 Key points—83
5.3.2 Epidemiology—83
5.3.3 Pathogen—84
5.3.4 Adverse events—84
5.3.5 Current/ongoing research—85
5.3.6 International developments—85
5.4 Meningococcal serogroup B disease—86
5.4.1 Key points—86
5.4.2 Epidemiology—86
5.4.3 Pathogen—87
5.4.4 Adverse events—87
5.4.5 Current/ongoing research—87
5.4.6 International developments—87
5.5 Meningococcal non-serogroup B and C types—88
5.5.1 Key points—88
5.5.2 Epidemiology—88
5.5.3 Pathogen—89
5.5.4 Adverse events—90
5.5.5 Current/ongoing research—90
5.5.6 International developments—90

6 Other possible future NIP candidates—91
6.1 Respiratory Syncytial Virus (RSV)—91
6.2 Tuberculosis—92
6.3 HIV/ AIDS—93
6.4 Hepatitis C—93
6.5 Clostridium difficile—94
6.6 Staphylococcus aureus—94
6.7 Pseudomonas aeruginosa—95
6.8 Group B Streptococcus—95

6.9 Cytomegalovirus—95
6.10 Norovirus—96
6.11 Others—96

References—99

List of abbreviations—117

Appendix 1 Vaccine coverage for infants targeted for HBV vaccination in the NIP, birth cohorts 2003-2011—121

Appendix 2 Mortality and morbidity figures per disease from various data sources—123

Appendix 3 Overview changes in the NIP since 2000—147

Appendix 4 Composition of vaccines used in 2012—157

Summary

This report presents current vaccination schedules, surveillance data and scientific developments in the Netherlands for vaccine preventable diseases (VPDs) which 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, W, A, X, Z, 29E)). Through the NIP, children in the Netherlands are offered their first vaccinations, DTaP-HBV-IPV-Hib (hepatitis B component included for children born on or after 1st August 2011) and pneumococcal disease (10-valent vaccine for children born on or after 1st March 2011) 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.
The Dutch Health Council recommended to harmonise the immunisation programme on the BES-islands (Bonaire, Sint Eustatius and Saba) with the European part of the immunisation programme in the Netherlands as much as possible.
The average participation for all vaccinations (except for HPV) included in the NIP was considerably over 90%. The participation among schoolchildren for MMR was below the WHO target of 95%. The immunisation coverage for three doses of HPV vaccination for adolescent girls was 56%.
Parents want to receive more information about the NIP in order to be able to make a well-considered decision about vaccination for their child.

Diphtheria
In 2011-2012, two cases of cutaneous diphtheria were reported in the Netherlands, both acquired in Gambia despite previous vaccination.

Pertussis
A large pertussis epidemic occurred in 2012 in the Netherlands, in particular affecting those above 8 years of age and unvaccinated infants. Similar large increases in notifications were observed worldwide. *B. pertussis* continues to change in ways that suggest adaptation to vaccination. The most recent change involves the emergence of strains which do not produce one or more components of pertussis vaccines.
The Dutch Health Council will give advice on possible additional preventive measures. The main focus of pertussis vaccination is to prevent severe pertussis in young, not yet fully vaccinated infants.

Tetanus
During 2011, five cases of tetanus in elderly, unvaccinated individuals occurred of which one was fatal. Based on cases occurring in 2011, there are indications that guidelines on post exposure prophylaxis are not well implemented in clinical care.

Poliomyelitis
In 2011 and 2012 (as per September,1) no cases of poliomyelitis were reported in the Netherlands, in the presence of efficient nationwide enterovirus (EV)

surveillance and an environmental surveillance programme in the traditional risk area with a high percentage of inhabitants that refuse vaccination for religious reasons.
A National Certification Commission for polio eradication was installed in 2011, as an independent body reporting to the European Certification Commission of the WHO on the absence of poliovirus circulation in the Netherlands based on data from national vaccination and surveillance activities.

***Haemophilus influenzae* serotype b (Hib) disease**
There have been no significant changes in the number of invasive disease cases caused by *Haemophilus influenzae* serotype b (Hib) in 2011 and 2012 in the Netherlands. Low antibody levels after the primary series, as found in PIENTER 2, have been confirmed in the study evaluating various pneumococcal vaccination schedules (PIM study).

Mumps
A mumps outbreak among students started late 2009 continued in 2010, 2011 and 2012. It is dominated by genotype G5 mumps virus. The number of reported cases in the season 2011-2012 was lower than in the previous season. The majority of the reported cases (72%) was fully (2xMMR) vaccinated. Sero-epidemiological results from the PIENTER 2 study (2006/7) showed waning immunity after both the first and second MMR and a susceptible group in the low vaccine coverage areas.

Measles
In total fifty measles cases were reported in 2011 of whom 34 were non-imported. The incidence of non-imported measles cases was 2,0/1.000.000, which is above the WHO elimination target (1 per million). Epidemiological and molecular investigation indicate that at least two third of the cases had been imported, mostly from within Europe, either directly or as a secondary case. One larger cluster (14 cases) was associated with a school with a low vaccination coverage. About a quarter of all reported cases in 2011 was hospitalised. Preparations to certify elimination of measles from the Netherlands are ongoing.

Rubella
The rubella incidence during 2011 was very low (2 cases; 0.12/million population).

Meningococcal serogroup C (MenC) disease
The incidence of Meningococcal serogroup C disease has strongly decreased since the introduction of vaccination in 2002; only three cases were reported in 2011.

Hepatitis B
The incidence of notified acute HBV infections dropped to an all time low since hepatitis B could first be diagnosed (late 1960s). The decrease is mainly attributable to a decrease in notifications in men who have sex with men (MSM). The number of cases with no information on risk exposure also declined. Screening of first generation migrants for chronic hepatitis B is likely to be cost-effective. Development of a national policy on this subject, also taking into account HCV, is a priority.

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 and in older age groups. The reduction in vaccine types has been partly counterbalanced by an increase in non-vaccine type IPD. The overall incidence decreased for 0-4 year-olds, but remained more or less stable for older age groups.
On basis of immunogenicity, the PIM study revealed that in the period between the primary series and the booster dose the 2-4-6 and 3-5 PCV-schedules were superior to the (Dutch) 2-3-4 and 2-4 schedule. However, after the booster dose at 12 months, all four immunisation schedules showed similar and protective antibody concentrations. When opting for a reduced dose schedule, the 3-5 schedule is the best choice, offering a high level of seroprotection against pneumococci.

Human papillomavirus (HPV)
Numbers of HPV-associated cancers have slightly increased in the last decade in the Netherlands.
In 2011, the reporting rate of adverse events was lower than in 2010.
In a study comparing characteristics of vaccinated and unvaccinated girls, it seems that routine HPV vaccination could reduce the inequity of prevention of cervical cancer.
Prevaccination data shows that the prevalence of HPV infection varies depending on the study population. The HPV prevalence amounted to 4.4% (highrisk HPV 2.7%) in girls aged 14-16 years in the general population to 72% (highrisk HPV 58%) in a high risk population (STI clinic, PASSYON study).
After the current vaccines that protect against 2 and 4 HPV-types and generate some crossprotection, currently new vaccines are developed that potentially give a broader protection.

Rotavirus
The rise in incidence of rotavirus-associated gastroenteritis seen in the Netherlands in the last few years did not continue in 2011. In 2011, G1[P8] was most commonly found in the Netherlands, followed by G9[P8] and G12[P8]. An international analysis of cost-effectiveness of rotavirus vaccination showed that it is highly sensitive to vaccine prices, rotavirus-associated mortality and discount rates, in particular that for QALYs. A model based upon Dutch data revealed that prematurity, low birth weight and congenital pathology were associated with increased severity and costs of rotavirus-associated gastroenteritis. Targeted RV vaccination was highly cost-effective and potentially cost saving from healthcare perspective; universal vaccination was only considered cost-effective when enclosing herd-immunity in the model.

Varicella zoster virus (VZV) infection
No striking changes occurred in the VZV epidemiology in the Netherlands in 2011. 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.
The incidence of GP consultations due to varicella in the Integrated Primary Care Information (IPCI) database is somewhat higher than according to routine surveillance data (CMR/LINH). However, with regard to patients requiring hospitalisation estimates from IPCI are comparable to routine surveillance data (LMR). These results confirm the somewhat lower disease burden due to varicella in the Netherlands compared to other countries.

Hepatitis A
In 2011, the number of hepatitis A infections (125 cases) is the lowest since monitoring started. Almost half of the Dutch cases (45%) were reported to be travel-related. For about one-third of the cases the most likely source of infection was contact with another infected person and for 18% of the cases food was the most likely source.

Meningococcal serogroup B disease
The incidence of meningococcal B disease has decreased further in 2011 (69 cases in 2011). A meningococcal B vaccine is currently under regulatory consideration (Bexsero, Novartis).

Men non-B and non-C
In 2011, 18 of the 89 meningococcal cases were non-serogroup B and C. The incidence of meningococcal serotype Y disease has increased further in 2011 in Europe and contributes up to 33% of the incidence in the USA. The number of meningococcal serogroup Y cases in the Netherlands was 15 in 2011 (vs. 11 in 2010).

Other possible future NIP candidates
Currently, two phase I vaccine trials against Respiratory Synstitial Virus (RSV) infection in infants are running. If the trials are successful, introduction of these vaccines on the market is not expected within the next five years. Cost-effectiveness analysis indicates vaccination of infants against RSV might be cost-effective.
Although BCG (Tuberculosis (TB) vaccine) 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. 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.
There is concrete evidence, since the discovery of Human immunodeficiency virus (HIV) in 1983, that a vaccine against HIV is potentially feasible. Vaccine candidates from different manufacturers are currently being tested in phase I or II clinical trials.
At present no vaccine is available to treat Hepatitis C virus (HCV) infection. Several companies are currently testing therapeutic vaccines in clinical trials.
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 vaccines to prevent congenital Cytomegalovirus (CMV) infection are under development. A norovirus vaccine has been tested in adults in a phase I trial.

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

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) 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), invasive pneumococcal disease, hepatitis B virus (HBV) and human papillomavirus (HPV) is included in the programme. The vaccines which are currently administered and the age of administration are specified in Table 1. Vaccinations within the NIP in the Netherlands are administered to the target population free of charge and on a voluntary basis.

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

Age	**Injection 1**	**Injection 2**
At birth (< 48 hours)	HBV [a]	
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 [b]	

[a] Only for children of whom the mother tested positive for HBsAg.
[b] Only for girls; three doses at 0 days, 1 month, 6 months.
Source:
http://www.rivm.nl/Onderwerpen/Onderwerpen/R/Rijksvaccinatieprogramma/De_inenting/Vaccinatieschema

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 with an increased risk of morbidity and mortality following an influenza virus 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 Centre for Infectious Disease Control (CIb), the Health Council and the KNCV Tuberculosis Foundation [1-4]. Besides HBV included in the NIP, an additional vaccination programme targeting groups at risk for HBV due to sexual behaviour or profession is in place in the Netherlands.

In 2010, Bonaire, Sint Eustatius and Saba became Dutch municipalities, together they are called the Dutch Caribbean. The existing vaccination programmes on the three islands were evaluated by the Dutch Health Council in 2012. The council recommended to add three vaccinations to the programme in order to protect the population adequately and thereby to harmonise the programmes between the Dutch Caribean and the European part of the Netherlands as much

as possible. It concerns vaccination against pneumococcal disease, meningococcal C disease and HPV. Furthermore, the Dutch Health Council recommended replacement of the oral polio vaccin with an inactivated vaccine which requires intramusculary administration for Bonaire. Furthermore, vaccination of risk groups against tuberculosis is recommended [5].
A limitation is the lack of data to assess the incidence of infectious diseases on these islands with a population too small for reliable estimates. The need for epidemiological data to evaluate the currect vaccination programme and to inform future programme changes was stressed.

The general objective of the NIP is the protection of the public and society against serious infectious diseases by vaccination. There are three ways of realising this objective. The first is the eradication of disease; this is feasible where certain illnesses are concerned (as seen with polio and smallpox) but not in all cases. Where eradication is not possible, the achievement of group or herd immunity is the next option. This involves achieving a level of immunity within a population, such that an infectious disease has very little scope to propagate itself, even to non-immunised individuals. To achieve herd immunity, a high general vaccination rate is neccesary. If this second strategy is not feasible either, the third option is to protect as many individuals as possible.
In the previous century, smallpox could be eradicated and nowadays the public health community is committed to the WHO target to eradicate polio by the year 2015. A further step is to reach the target, set by WHO/Europe, to eliminate measles and rubella by 2015. 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. This 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 chapter.

2 Surveillance methodology

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

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 which 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 ten 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 2 for the period of notification per disease [6].

Table 2 Periods of notification for vaccine preventable diseases, included in the National Immunisation Programme

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

[a] For infants only.

In December 2008, a new law was set up which required the notification of all NIP targeted diseases. From that time physicians, laboratories and heads of

institutions 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 [7]. 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) 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. Until 2010, the LMR was managed by the research institute Prismant and from 2011 Dutch Hospital Data managed the hospital data. 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[8].
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 [9] 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 [9]. 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 [10]. 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 for 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 (IBD) 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 information regularly. Aggregated results are shown on the RIVM website. It is important to keep in mind that the presence of a 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 [11] (n_{blood}=10,128) and 2006-2007 [12] (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) [13].

2.5 Surveillance of adverse events following vaccination

Passive safety surveillance through an enhanced spontaneous reporting system was in place at RIVM until 2011. Aggregated analysis of all reported AEFI was published annually. The last report over 2010 also contains a detailed description of the methodology used and a review of trends and important findings over the last 15 years [14].
From 1st January 2011 this enhanced spontaneous reporting system of adverse events following immunisation (AEFIs) was taken over by the Netherlands Pharmacovigilance Centre (Lareb). Detailed information is available at www.lareb.nl.
Due to this transition, comparisons between 2010 and 2011 should be made with caution. Furthermore, Lareb started a campaign in 2011 among parents of vaccinated children to promote the reporting of AEs.
Furthermore, CIb performes systematic studies to monitor the safety of the NIP, for instance questionnaire surveys and linkage studies.

2.6 Vaccine effectiveness

Vaccine effectiveness (VE) can be estimated using the 'screening method' with the following equation:

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

PCV = proportion of cases vaccinated, PPV = proportion of population vaccinated, and VE = vaccine effectiveness

3 Vaccination coverage

E.A. van Lier, L. Mollema

Just like previous years, the average participation in 2012 for all vaccinations (except HPV) included in the NIP was at national level considerably above 90%. The lower limit of 95%, set by the WHO as target for MMR vaccination, was not yet reached for schoolchildren (93%).
These results are published in a report by the RIVM on the vaccination coverage in the Netherlands in 2012. The report included data on newborns born in 2009, toddlers born in 2006, schoolchildren born in 2001 and adolescent girls born in 1997 (Table 3) [15].
For babies, the participation for the MMR, Hib and meningococcal C vaccination amounted to 96%, for the DTaP-IPV and pneumococcal vaccination up to 95%. The participation among schoolchildren for DT-IPV and MMR was with 93% somewhat higher than in the previous year. The 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 56%.
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 children in the Netherlands are vaccinated on time and in full.

Table 3 Vaccination coverage per vaccine for age cohorts of newborns, toddlers, and schoolchildren in 2006-2012

	Newborns*						
Report Year	**cohort**	**DTaP -IPV**	**Hib**	**Pneu ** **	**MenC**	**MMR**	**HBV[a]**	**HBV[b]**
2006	2003	94.3	95.4	-	94.8	95.4	86.7	90.3
2007	2004	94.0	95.0	-	95.6	95.9	88.7	92.3
2008	2005	94.5	95.1	-	95.9	96.0	90.7	97.4
2009	2006	95.2	95.9	94.4	96.0	96.2	92.9	95.6
2010	2007	95.0	95.6	94.4	96.1	96.2	94.2	97.2
2011	2008	95.4	96.0	94.8	95.9	95.9	94.8	96.6
2012	2009	95.4	96.0	94.8	95.9	95.9	94.3	96.1

	Toddlers*		Schoolchildren*			Adolescent girls*	
Report Year	**cohort**	**DTaP -IPV**	**cohort**	**DT -IPV**	**MMR *** **	**cohort**	**HPV**
2006	2000	92.5	1995	93.0	92.9		
2007	2001	92.1	1996	92.5	92.5		
2008	2002	91.5	1997	92.6	92.5		
2009	2003	91.9	1998	93.5	93.0		
2010	2004	91.7	1999	93.4	93.1		
2011	2005	92.0	2000	92.2	92.1		
2012	2006	92.3	2001	93.0	92.6	1997	56.0

* Vaccination coverage is assessed at ages of 2 years (newborns), 5 years (toddlers), 10 years (schoolchildren) and 14 years (adolescent girls).
** 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.

3.1 Acceptance of vaccination

CIb is currently performing a project in collaboration with the University of Maastricht aiming to develop a monitor of the determinants of acceptance of vaccination for both parents and childhood vaccine providers (CVPs). With an appropriate monitoring system, trends can be followed and innovative measures can be taken to intervene in time in case the acceptance of vaccination is decreasing. This is important because the overall compliance does not give information on the (changing) motivation to vaccinate or not. Parents who comply with the programme might already have some doubts. Unexpected factors from outside the NIP can influence and alter the attitude towards vaccination quickly, e.g. epidemics, media, disagreeing professionals and anti-vaccination lobbying.
In order to know what the possible determinants are, online focus groups with parents who (partly) refused vaccinations for their children (0-4 years old) and face-to-face focus groups with parents visiting anthroposophical child welfare centres (CWCs) have been performed. Results showed that factors that influenced their decision to refuse vaccination were: a healthy lifestyle, perceived low vaccine efficacy, perceived low risk of getting a disease, perceived advantages of experiencing the disease, high risk perception of vaccination side

effects, negative experience with vaccination, strong perception of a good health of their child, doubts about components of the vaccine and low trust in institutions [16, 17]. Both groups had a need for more information [16, 17]. Face-to-face focus groups have also been performed with parents of different ethnic backgrounds (like Moroccan or Turkish). Results showed parents had a positive attitude towards childhood vaccination and a high confidence in advices of the CVPs. Parents regarded vaccination as self-evident and important, perceived low social norms and no practical barriers. Parents perceived a language barrier in understanding provided NIP-information and had a need for more NIP-information [18]. The data above will be used to develop questionnaires in order to determine the most important factors associated with the intention to vaccinate for parents and how satisfied the CVPs are with the NIP.

4 Current National Immunisation Programme

4.1 Diphtheria

F. Reubsaet, G.A.M. Berbers, C.W.G. Hoitink, F.R. Mooi, J.M. Kemmeren, N.A.T. van der Maas

4.1.1 Key points

- In 2011-2012, two cases of cutaneous diphtheria were reported in the Netherlands, both acquired in Gambia despite previous vaccination.

4.1.2 Changes in vaccine 2011-2012-2013

In 2012, no changes in diphtheria containing vaccines, used in the National Immunisation Programme were implemented. All infants receive a primary series of hexavalent DTaP-IPV-Hib-HepB (Infanrix hexa; GSK). The booster dose at four years of age is DTaP-IPV (Infanrix; GSK) and at nine years of age DT-IPV (NVI).

4.1.3 Epidemiology

In 2011 and 2012 up till week 35 two diphtheria notifications were received. The first was a 60 year old male with cutaneous diphtheria, the second was a 64 year old female, also with cutaneous diphtheria. Both persons were vaccinated and both travelled to Gambia.

4.1.4 Pathogen

From week 33, 2011 till week 35, 2012, the RIVM received six *Corynebacterium diphtheriae* strains, all with suspicion of cutaneous diphtheria. One patient with an unknown travelling history, one patient with no permanent home, but originally from Eastern Europe, and two patients who had visited respectively the Philippines and Cambodia-Thailand had diphtheria-toxine-PCR negative strains. The two patients who travelled to Gambia had diphtheria-toxine-PCR positive strains; one of them had a low diphtheria antibody concentration (0.011 IU/ml). The level of antibodies of the other patient is unknown, but he indicated to have received his regular vaccinations and a booster vaccination in 2006.

4.1.5 Adverse events

Transcutaneous immunisation (TCI) is a non-invasive and easy-to-use vaccination method. Hirobe et al. showed in a clinical study this TCI formulation induces an immune response without severe adverse reactions in humans [19].

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

Thirty European countries regularly send surveillance data on diphtheria to the European Centre for Disease Control (ECDC). This information is available on the ECDC-website (http://www.ecdc.europa.eu/en/activities/surveillance/EDSN/Pages/index.aspx). No relevant outbreaks have occurred in 2011 and 2012.

4.2 Pertussis

N.A.T. van der Maas, J.M. Kemmeren, A.K. Lugner, A.W.M. Suijkerbuijk, A. Buisman, G.A.M. Berbers, M.A.C. de Bruijn, C.A.C.M. van Els, H.E. de Melker, F.R. Mooi

4.2.1 Key points

- A large pertussis epidemic occurred in 2012 in the Netherlands in particular affecting those above eight years of age and unvaccinated infants. Similar large increases in notifications were observed worldwide.
- Age groups (i.e. between six months and eight years of age) targeted with both ACV in the primary series and booster at four years of age had lower incidences.
- About three years after the booster dose vaccine-effectiveness estimates decreased, resulting in increased incidence from eight years onwards.
- *B. pertussis* continues to change in ways that suggest adaptation to vaccination. The most recent change involves the emergence of strains which do not produce one or more components of pertussis vaccines.
- The Dutch Health Council will advice on possible additional preventive measures. The main focus of pertussis vaccination is to prevent severe pertussis in young, not yet fully vaccinated infants.

4.2.2 Changes in vaccine 2011-2012-2013

No changes in the pertussis containing vaccines used were implemented during 2012. See section 4.1.2.

4.2.3 Epidemiology

4.2.3.1 Disease

Since the sudden upsurge of pertussis in 1996 [20], the incidence of reported and hospitalised pertussis cases has remained high. Peaks in reported cases are observed every two to three years. However, the trend in 2011 and 2012 was distinct from previous years. Following the normal rise of notifications in late summer and autumn of 2011, instead of the expected decrease, numbers increased. A decline was only visible from September 2012 onwards. Further, compared to other years with increased notifications, like 2001, 2004, 2007 and 2008, numbers for 2012 were higher (Figure 1).

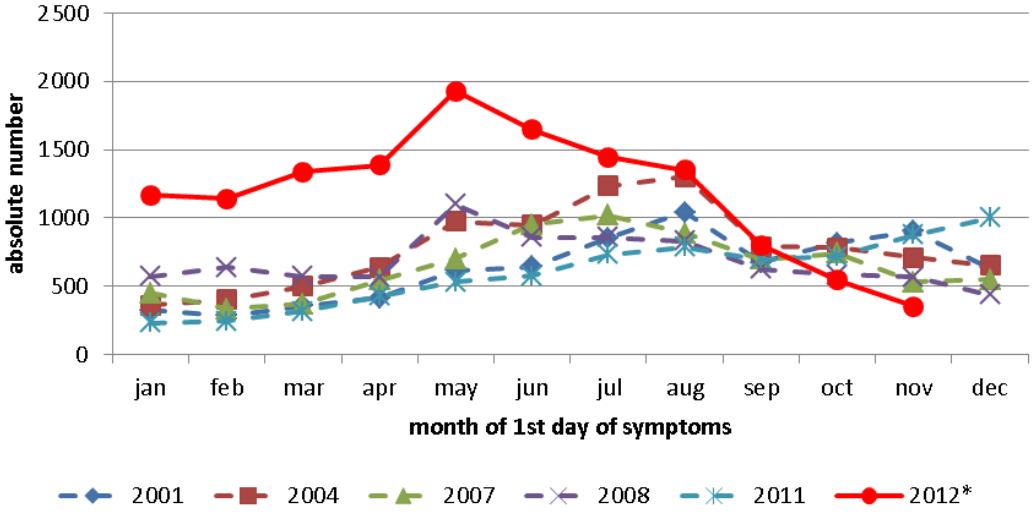


*Figure 1 Absolute number of notifications per month for 2001, 2004, 2007, 2008, 2011 and 2012. *=reports till January 5th 2013 included.*

Age specific incidence rates (IR) for infants of 0-2 months of age, children eight years and older, adolescents and adults were higher than in previous years with high disease rates (Figure 2). However, we must bear in mind that data from 2012 are restricted to a limited period with high notifications, whereas data from previous years are based on the peak period and a period of lower notifications.

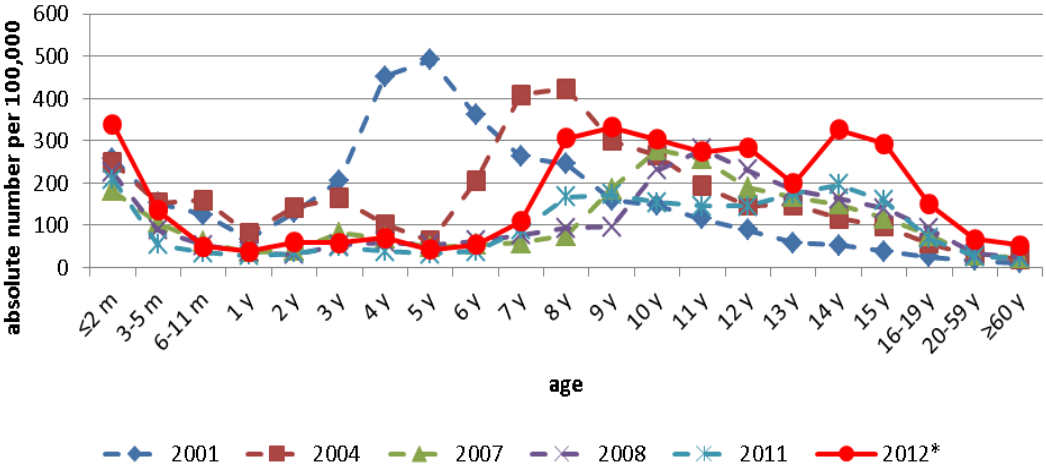


*Figure 2 Age specific incidence per 100,000 for 2001, 2004, 2007, 2008, 2011 and 2012. *=reports till January 5th2013 included.*

Figure 2 reflects the effect of the measures, taken to reduce pertussis burden. Before the introduction of the booster dose with acellular pertussis vaccine, November 2001, a peak in IR was seen in 4-6 year old children (line '2001'). In the following years, this peak shifted to older age categories. Furthermore, IRs in infants in the age category three months to four years were higher in 2001 and 2004, when the whole cell vaccine was used for the primary series, compared to later years when acellular vaccines were used (lines '2007', '2008', '2011' and '2012').

As mentioned in the previous report [21], the positive impact of the measures mentioned above, is also visible in the hospitalisation rates, retrieved from the National Medical Registration (LMR). IRs of infants under one year of age showed a decreasing trend from 2001 onwards. IRs for older children, adolescents and adults are ≤ 1 per 100,000 (Figure 3). However, overall IR for hospitalisations increased from 0.57 per 100,000 in 2010 to 0.76 in 2011, similar to the increase in notifications in 2011.

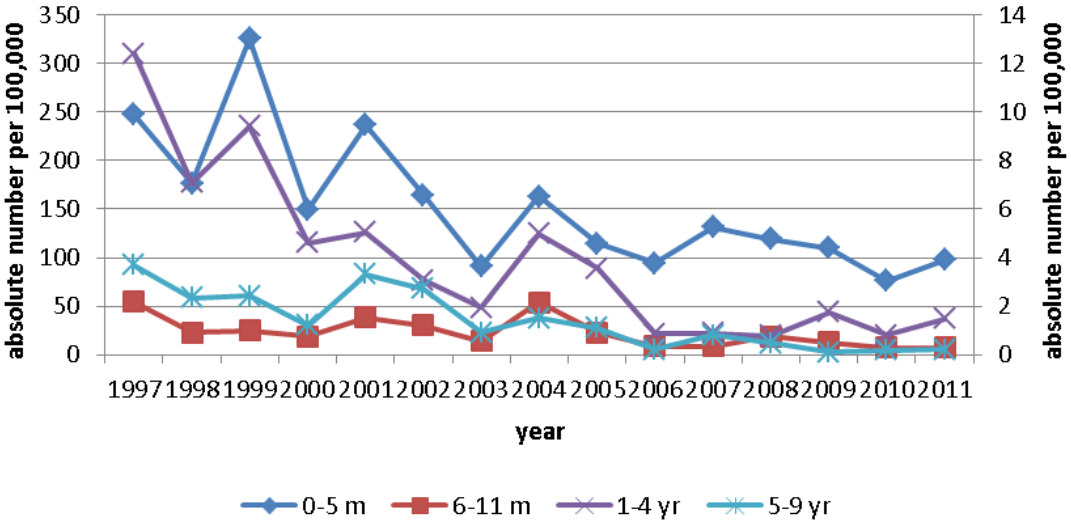


Figure 3 Incidence rates per 100,000 for hospitalisations of 0-5- and 6-11-month-olds and 1-4- and 5-9-year-olds in 1997-2011.

The trend in decreasing hospitalisation due to the change to an acellular vaccine is also observed in data on hospitalisation within the notifications (Table 4). For the 3-5 month and 6-11 month old infants, IRs before 2005 were higher than in later years. The year 2012 does not follow this trend, but again must be noted that these rates are based on a part of the year compared to a full calendar year for 2001-2011.

Table 4 Incidence per 100,000 of hospitalisations within the notifications for 2001, 2004, 2007, 2008, 2011 and 2012.

	2001	**2004**	**2007**	**2008**	**2011**	**2012##**
0-2 months	126	189	160	173	152	265
3-5 months	58	52	33	38	28	65
6-11 months	19	26	3	13	5	7

##=Reports until August 25th included.

In 2011, an 85-year-old man and a 0-month-old infant died from pertussis. In early 2012, a twin of 1 month old died due to pertussis.

4.2.3.2 Vaccine effectiveness

In Table 5, vaccine effectiveness (VE) for the infant vaccination series is shown. For some age groups, the proportion of vaccinated cases exceeded the vaccine coverage of the population (96%). Therefore, VE could not be estimated (indicated by '-'). We would like to emphasise that the presented VE should not be interpreted as 'true' absolute efficacies. They are used to study trends in VE estimations. After the replacement of the whole cell vaccine by an acellular vaccine in 2005, the VE for children aged 1-3 years increased, probably due to a

better protection of this group conferred by the acellular vaccine. This is in line with data on incidence rates and hospitalisation, all indicating the benefit of this transition.

Table 5 Estimation of vaccine effectiveness of the primary series of infant vaccinations by the 'screening method' for 1-3-year-olds per year[a]

Age	'93	'94	'95	'96	'97	'98	'99	'00	'01	'02	'03	'04	'05	'06	'07	'08	'09	'10	'11
1yr	94	77	92	32	29	38	63	78	73	63	29	54	72	87	92	90	90	97	97
2yr	92	58	42	63	-	33	22	52	46	41	-	-	67	58	92	91	89	93	91
3yr	94	79	60	38	-	9	-	-	-	54	10	37	59	43	84	82	83	89	88

[a] In 2005 the whole cell vaccine was replaced by an acellular vaccine.

VE for the booster dose at four years of age decreases after ~4 years, i.e. when children reach the age of eight years, especially when infection rates are high (Table 6). Since the introduction of the booster (from birth cohort 1998 onwards), three different vaccines were used, one with a low dose of antigen and two containing high antigen doses. Comparison between different vaccine is not possible due to short surveillance duration after implementation and due to different primary series (whole cell vs acellular pertussis) used and changing infection rates over the years.

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

Age/reporting year	'04	'05	'06	'07	'08	'09	'10	'11
5yr	77	71	82	86	80	84	83	92
6yr	74	70	80	79	71	61	89	87
7yr		68	57	68	71	51	61	67
8yr			67	75	56	47	35	72
9yr				73	63	36	49	37
10yr					60	-	13	26
11yr						-	11	-
12yr							45	-
13yr								1

For some age groups, the proportion of vaccinated cases exceeded the vaccine coverage of the population (92%). Therefore, VE could not be estimated.
Two recent Californian studies revealed an unexpected low VE of the acellular booster given at the age of 4-6 years [22, 23]. In both studies children were vaccinated with acellular vaccines at the ages of 2, 4, 6 and 15-16 months and 4-6 years. In one study [23], VE effectiveness was 41% and 24% for children aged 2–7 years and 8–12 years respectively. The second study [22] showed protection against pertussis waned during the five years after the fifth dose of pertussis vaccine to approximately 71%.

4.2.3.3 Cost-effectiveness

Recently, three economic evaluations on pertussis vaccination have been published, of which two were focused on the Dutch population and one on the Canadian population [24-26]. With regard to the various vaccination strategies, CIb has calculated additional cost-effectiveness ratios. Here the cost-effectiveness ratios are presented for the health care costs; production losses due to illness are not included.
Westra et al. evaluated the cost-effectiveness of three pertussis vaccination strategies. Based on Dutch incidence and cost data, the authors concluded that neonatal vaccination would not be cost-effective, with a cost-effectiveness ratio

of more than € 300,000/QALY gained [24]. Additional preliminary calculations performed by CIb confirm this strategy would not be cost-effective for the Dutch situation (>€ 600,000/QALY gained).
In addition, Westra et al. found a maternal vaccination strategy could be cost-effective (€ 3,500/QALY gained) in the Netherlands [24]. The reason this strategy would be more cost-effective than the neonatal strategy is due to the QALY gain of the averted infections in mothers. This result is based on an assumed underreporting of 200 times the notifications of adults, and QALY loss also in the underreported cases. With less underreporting and lower QALY loss in the underreported cases, the cost-effectiveness becomes less attractive. Preliminary calculations made by CIb show unfavourable cost-effectiveness ratios (> € 100,000/QALY gained). Finally, Westra et al. found cocooning could be cost-effective mainly due to the beneficial effects for the parents, assuming a 200 times underreporting with a QALY gain in the averted adult cases [24]. However, preliminary results of a cost-effectiveness analysis performed by CIb shows that the cocooning strategy could reduce the disease burden in infants and mothers vaccinated, but the costs involved are high according to acceptable cost-effectiveness thresholds (> € 100,000/QALY gained). Including fathers in the vaccination would cost even more per QALY gained. Differences in results between the Dutch studies are caused by different assumptions, mainly regarding the factor underreporting (100 vs. 200 times, i.e. one out of 100 vs. 200 cases notified) and the QALY losses due to length of symptomatic illness (6 weeks vs. 3 months).
Another recent Dutch cost-effectiveness analysis, using a dynamic model of pertussis booster vaccination strategies of one cohort of adolescents, concludes a pertussis booster strategy in young adolescents could be considered cost-effective in preventing pertussis [25]. In those analyses, the underreporting was assumed to be about 600 times the notified cases; also assumed was a two-year's full immunity and ten years partial immunity. The model predicted, due to vaccination of adolescents, the number of symptomatic cases would increase in adults and elderly, causing both QALY loss and production losses in these age groups.
A Canadian study shows cost-effectiveness of immunising health care workers in paediatric health care centres [26]. No data on cost-effectiveness for the Netherlands are available. We assume cost-effectiveness is not favourable because in our country infants do not go to day care centres before three months of age; at that time they have been vaccinated at least once.

4.2.4 Pathogen

As observed in previous years, P3 *B. pertussis* strains predominated in 2012. These strains were found at a frequency of 92% (range 64% to 100%) from January 2004-August 2012. P3 strains produce more pertussis toxin than P1 strains, which predominated in the 1990s; there is some evidence this has increased the severity of pertussis infections [27, 28]. 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 [29, 30]. Like the P1 strains, P3 strains show (small) differences in antigenic make-up in pertussis toxin and pertactin compared to the pertussis vaccines [31]. A notable trend observed in the last five years, the replacement of serotype 3 strains by serotype 2 strains, may be reversing, as now serotype 3 strains are increasing in frequency, from 13% in 2011 to 18% in 2012. We presume these changes are mainly driven by population immunity due to infection. Thus, high frequencies of one serotype will result in population immunity against this serotype providing a selective advantage for the serotype

which occurs in low frequencies, a phenomenon known as frequency-dependent selection. A worrying development is the emergence of strains, which do not produce one or more vaccine components, in particular pertactin and filamentous hemagglutinin (respectively, Prn- and FHA-vaccine antigen deficient (VAD) strains). FHA- and Prn-VAD strains have been identified in France, Japan, Finland, Sweden and the Netherlands in frequencies ranging from 2-26% [32, 33] (our unpublished data). Before 2010, VAD strains were not detected in the Netherlands. In 2010, 2011 and 2012, between 4% and 5% the *B. pertussis* population in the Netherlands was composed of Prn- and FHA-VAD strains. Currently used acellular vaccines in the Netherlands all contain both Prn and FHA, besides Ptx; it seems reasonable to assume they are less effective against VAD strains.

4.2.5 Adverse events

The enhanced passive surveillance system, from January 2011 onwards in place at 'Lareb', receives reports of Adverse Events Following Immunisation (AEFI) for all vaccines included in the NIP. In 2011, reports following infant doses of DTaP-IPV-Hib (or DTaP-Hib-IPV-HepB after 1/8/2011), scheduled at 2, 3, 4 and 11 months, amounted to 50% (n= 554) of the total number of reports [34]. The number of reports in 2011 is somewhat lower than the range of numbers in the time-period 2005-2010 (i.e. 593-756). This may be caused by the transition of the surveillance system from the RIVM to Lareb at 1/1/2011. However, the total number of reported adverse events was similar, indicating the transition went well. For the fourth consecutive year, AEFI after the DTaP-IPV booster vaccination at four years of age were most frequent (n=280, 25%), mainly concerning local reactions with of without fever.
Several studies assessed the safety of combined DTaP-IPV vaccines for primary and booster vaccination in children. All vaccines (quadrivalent [35], pentavalent [35-38] as well as hexavalent vaccines [39-42] showed a good safety profile when given separately or co-administered with a pneumococcal vaccine (PCV7) [43, 44], or MMR with or without varicella vaccine.45, 46 One study assessed the safety of mixed primary infant schedules [47]. It showed a mixed 2-, 4-, 6-month pentavalent infant vaccine schedule had higher reactogenicity. This suggests it may be preferable to complete the primary infant vaccine series with the same vaccine, rather than considering infant vaccines as interchangeable. Three studies showed TdaP vaccine was safe as a booster in adolescents, adults and elderly [48-50]. The same results were found in a VAERS review among pregnant women [51] and adults aged >= 65 years [52].
Since the development cost of acellular pertussis vaccines are higher, the production more complex and the efficacy less durable then expected, whole cell DTP (DTwP) is still used in many immunisation schedules, especially in developing countries. In a phase III trial in India, the safety of a newly developed semi-synthetic DTwP vaccine was assessed in comparison with the standard commercially available and routinely manufactured DTwP vaccine. It showed a significant lower incidence of local AEs in comparison to the routine vaccine [53].

4.2.6 Current/ongoing research

The efficacy of the current vaccination programme and the effect of recent changes in vaccines will be monitored based on hospitalisations and notifications. Currently we are studying the possible association between local adverse reactions (ARs) and high cellular immune responses following the booster dose at four years of age. Studies on cellular immunity after pertussis vaccination have shown the change from cellular to acellular vaccine in 2005 has

raised the T-cell responses after the primary vaccinations. There was a slight shift in the T-cell balance from T-helper-1 cells to T-helper-2 cells. Furthermore, IgG4 en IgE antibodies are induced by acellular vaccines [54]. These shifts in immune responses may be associated with more allergic reactions [55-57]. The transition to acellular DTP-IPV-Hib in 2005 resulted in an increase of the risk of (severe) local and systemic reactions after the booster dose at the age of four, thus after the 5th acellular dose [21, 58]. The height of the T-cell responses, the disturbance of the balance between Th1- and Th2-cells after four high dose acellular vaccines and the increase in AEFI after the preschool (5th) booster vaccine may be related. The RIVM and the Netherlands Pharmacovigilance Centre 'Lareb' recently have started a case-control study into this relationship. Overall, it should be noted that, despite the side effects of the booster vaccination, acellular vaccines are less reactogenic than whole cell vaccines [59].
The genomes of a number of *B. pertussis* strains, isolated in 2012 epidemic, have been sequenced to identify possible bacterial factors which may have contributed to the anomalous epidemic. Conclusions await bioinformatic analyses of these genome sequences. In collaboration with EU partners and with support from the ECDC we are comparing vaccination policies, pertussis burdens and the structure of *B. pertussis* populations between a number of EU countries. Preliminary findings suggest vaccinations policies affect the emergence of VAD strains, pointing to future interventions to alleviate this problem.

4.2.7 International developments

The increase in pertussis, observed in 2012, not only occurred in the Netherlands, but in many developed countries, including the UK and USA [23, 60]. Both countries have responded in several ways. The Joint Committee of Vaccination and Immunisation for England and Wales is studying the effects of different interventions, including a booster dose in teenagers and vaccinating pregnant women, health care workers, neonates, or close contacts of neonates [60]. Recently, the UK has recommended a pertussis vaccination for all pregnant women in the third trimester (http://www.nhs.uk/conditions/pregnancy-and-baby/Pages/Whooping-cough-vaccination-pregnant.aspx). This is a temporary measure, only to decrease disease burden in very young infants. In the US, the Advisory Committee on Immunization Practices (ACIP) has updated recommendations for use of acellular pertussis vaccine (Tdap) in pregnant women and persons who have close contact with an infant aged <12 months. The CDC has initiated a study to conduct enhanced (strain) surveillance of pertussis and other *Bordetella* species [61]. Studies evaluating TdaP effectiveness and duration of protection in adolescents fully vaccinated with DTaP are being conducted in Washington and California [61]. Public awareness efforts have focused on informing residents about the signs and symptoms of pertussis and vaccination recommendations.
A new promising approach to improve immunity against pertussis is the development of a live vaccine based on an attenuated *B. pertussis* strain [62]. This vaccine is applied intranasally and is undergoing phase I clinical trials. Evidence from the field suggests that immunity induced after infection lasts longer than immunity induced after vaccination [63] and indeed mice experiments showed that immunity induced by the live pertussis vaccine persists longer compared to acellular vaccines [64]. Furthermore, the live vaccine seems to induce a broader immunity as, in contrast to acellular vaccines, it also protects against *B. parapertussis* in mice [65]. A live pertussis vaccine may be used for neonatal vaccination, although safety issues need to be addressed first. In addition, live vaccine may be used for adolescent and adult boosters, or

during outbreaks. Apart from safety issues (e.g. safety in immune-compromised hosts), one question which should be resolved is how fast protective immunity is induced by the live vaccine.

4.3 Tetanus

S.J.M. Hahné, H.E. de Melker, C.W.G. Hoitink, D.W. Notermans, J. Kemmeren

4.3.1 Key points

- During 2011, five cases of tetanus in elderly, unvaccinated individuals occurred of which one was fatal.
- Based on cases occurring in 2011, there are indications that guidelines on post-exposure prophylaxis are not well implemented in clinical care.
- A study to assess whether a bed-side tetanus immunity test can improve this has been started end of 2012.

4.3.2 Changes in vaccine 2011-2012-2013

From August 2011 onward all infants receive Infanrix Hexa (GSK) for the primary vaccinations at 2, 3, 4 and 11 months of age, together with a dose of pneumococcal vaccine.

4.3.3 Epidemiology

During 2011, five cases of tetanus have been notified 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.
The incidence of reported tetanus in the Netherlands is displayed in Figure 4. In 2012, up to week 38, one case of tetanus was reported in a 21 year old after a dog bite. The person had been fully vaccinated except for the booster at nine years of age.

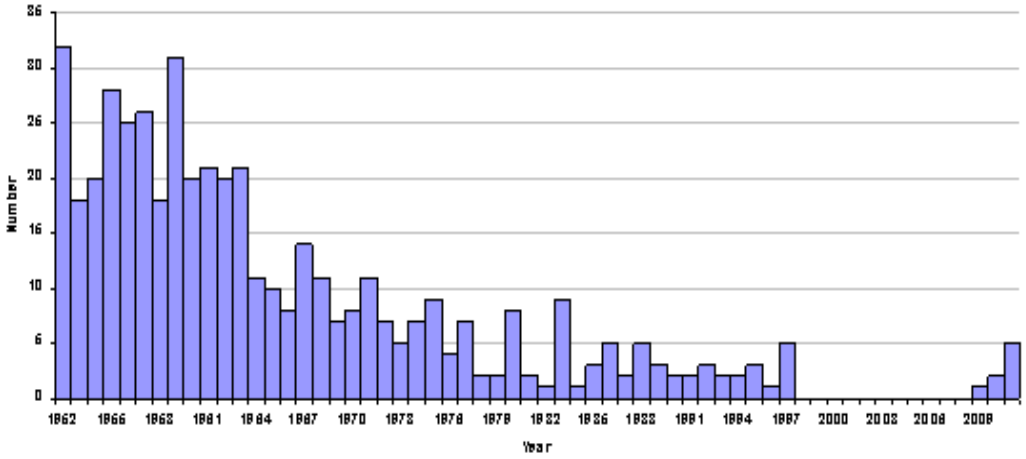


Figure 4 Reported cases of tetanus in the Netherlands by year, 1952-2011. Note: between 1999 and 2009 tetanus was not notifiable.

4.3.4 Pathogen

In none of the reported cases, a *Clostridium tetani* isolate was recovered for characterisation, which is usual for tetanus.

4.3.5 Adverse events

See section 4.1.5 and 4.2.5.

4.3.6 Current/ongoing research

The history of cases reported in 2010 and 2011 suggests TIG as part of post-exposure prophylaxis may not be provided adequately in the Netherlands. On the other hand, tetanus vaccination may be given more often than needed. The choice of tetanus prophylaxis for patients with injuries depends on their vaccination history, which has been demonstrated to be unreliable. The use of a rapid immunoassay may improve the evaluation of tetanus immunity and thus help to avoid inadequate prophylactic measures and reduce costs. To do so, the tetanus quick stick (TQS) has been developed. The TQS was evaluated by Stubbe et al. [66] in an emergency department including a cost-effectiveness analysis. In this Belgian prospective, double-blind multicentre study, 611 adult patients with a wound were included. The TQS test was performed by a nurse before the vaccination history was taken and the choice of prophylaxis was made, using the official algorithm (Belgian Superior Health Council) by a doctor who was unaware of the TQS result. The prevalence of protective anti-tetanus immunity was 74.1%. Immunity was lower in older patients and in female patients. The TQS proved to be a cost-effective tool for patients presenting with a tetanus-prone wound who were considered to be unprotected from their vaccination history. The use of the TQS would have improved management in 57% of patients by avoiding unnecessary treatments, leading to a small reduction in the mean cost per patient (€ 10.58 per patient with the TQS versus € 11.34 per patient without). The benefits of the TQS use were significantly greater in patients younger than 61 years old: unnecessary treatment would have been avoided in 76.9% of cases and the mean cost per patient reduced to € 8.31. Stubbe concludes that in selected patients, the TQS is a cost-effective tool to evaluate tetanus immunity. She proposes an algorithm for emergency department assessment of tetanus immunity integrating age and the TQS result. A recent study from the UK also concluded using a TQS can improve clinical management and may even be cost-saving [67].

To study the benefits of the TQS in the Netherlands, RIVM-CIb-EPI in collaboration with LCI and three hospitals have initiated a research project that has been started late 2012. The objective of the study is to assess whether TIG and revaccination prescription is in accordance with the immune status of a patient as measured by the TQS. The secondary objective is to assess whether or not the TQS might be of additional value in decision making for prophylaxis for specific age groups.

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 2011 and 2012 (as per 1st September) no cases of poliomyelitis were reported in the Netherlands, in the presence of efficient nationwide enterovirus (EV) surveillance and an environmental surveillance programme in the traditional risk area with a high percentage of inhabitants that refuse vaccination for religious reasons.
- A National Certification Commission for polio eradication was installed in 2011, as an independent body reporting to the European Certification Commission of the WHO on the absence of poliovirus circulation in the Netherlands based on data from national vaccination and surveillance activities.
- India has been removed from the list of polio endemic countries in 2012 as the last case of wild polio was reported on January 13, 2011 from West Bengal. Extended Acute Flaccid Paralysis (AFP) and environmental surveillance has proven the absence of wild polio virus circulation in India for more than one and a half year.

4.4.2 Changes in vaccine 2011-2012-2013

No changes in the inactivated poliomyelitis virus (IPV) containing vaccines used, were implemented during 2012. See section 4.1.2.

4.4.3 Epidemiology

4.4.3.1 Polio eradication initiative: global situation in 2012.

The biggest achievement of the polio eradication initiative until now is stopping wild poliovirus circulation in India, the country that traditionally reported most cases of polio in the world and where eradication yet could be achieved by systematic application of multiple series of vaccination rounds per year with trivalent OPV and later on with bivalent type 1 and 3 OPV. Eradication of polio from India gives hope for global polio eradication in the near future.

Poliomyelitis remained endemic in Afghanistan, Nigeria and Pakistan. Persistent wild poliovirus (WPV) transmission in Afghanistan is largely restricted to districts in three provinces in the south of the country. The last case had onset of paralysis on 21 July (WPV1), amounting to a total of seventeen cases in 2012. In Pakistan, WPV transmission is also restricted to three groups of districts. The total number of cases in 2012 (until September) remains 29 with the most recent case of WPV1 on 21 July. In addition, Afghanistan and neighbouring Pakistan repeatedly re-infect one other due to the substantial population movements within and between the countries. In both countries political and social unrest is interfering strongly with optimal performance during vaccination activities; yet progress is made, but slowly in recent months.
Nigeria is one of the most entrenched reservoirs of wild poliovirus in the world, with ongoing transmission of WPV1, WPV3 and vaccine-derived poliovirus (VDPV) type 2. The total number of cases reported in 2012 up to September is 77. Successful application of vaccination activities in the past have brought eradication near, but complacency and political unrest as well as incompetent leadership at all levels are impeding with progress needed to finish the job.

Furthermore, the disease has re-established transmission in Angola, Chad and the Democratic Republic of the Congo, who were previously polio-free. In Angola, no cases have been reported in 2012 until September. In 2011 five cases were reported, the last case had onset of paralysis in July 2011. In Chad, the number of reported cases in 2012 is five (until September). In the Democratic Republic of the Congo, no WPV cases have been reported in 2012. However, VDPV2 was reported in seventeen cases.
Due to persistence of imported WPV or VDPV circulation for more than twelve months, both Chad and the Democratic Republic of the Congo are classified as having re-established transmission.
Several more countries had ongoing outbreaks in 2011 due to importation op poliovirus (http://www.polioeradication.org/Infectedcountries.aspx).

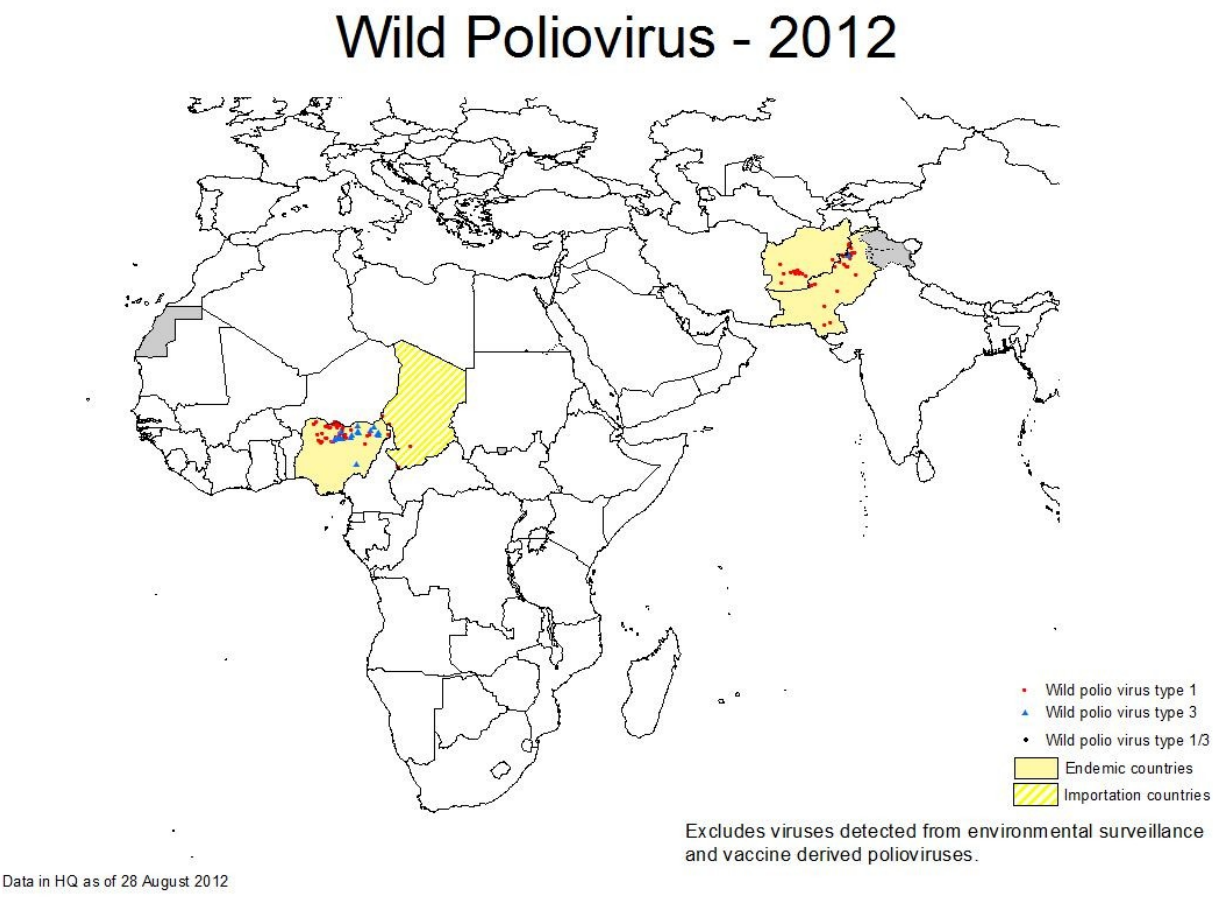


Figure 5 Wild poliovirus cases worldwide.

4.4.3.2 Serosurveillance

In 2006-2007, a large serosurvey was performed with collection of serum and questionnaire data of a random sample (n≈8000) of 0-79 year old Dutch inhabitants (PIENTER 2) [12]. Within this group, oversampling of non-Dutch inhabitants was performed. Furthermore, persons living in the area with known low vaccination coverage (LVC) were asked to participate. Aim of this survey was to assess age specific seroprevalence rates of all diseases, targeted by the NIP. For poliomyelitis, a neutralisation test (NT) was used.

In the nationwide sample (NS) seroprotection rates were 94.6%, 91.8% and 84.0% for poliovirus type 1, 2 and 3 respectively, corresponding with mean 2log titers (95%CI) of 7.42 (7.34-7.50), 6.94 (6.83-7.05) and 6.01 (5.89-6.12).
In 0-7 month old infants seroprotection rates were 85.7%, 80.2% and 80.0% for the three respective serotypes. An increase in seroprotection was seen, due to a booster dose at 11 months and 4 years of age. Seroprotection was highest in 5 year olds (100% for type1 and 2) and 9-10 year olds (96% for type3). Seroprevalence of 10-44 year old people with a completed NIP and no revaccinations listed was 98.8%, 97.5% and 90.9% for the three serotypes, respectively. This reflects a high and long-lasting protection against poliomyelitis after a completed NIP.
In the subgroup of orthodox reformed people within the LVC, mostly refusing vaccination on religious grounds, seroprevalence rates were 58.2%, 54.4% and 55.4% for the respective serotypes. Mean 2log titers (95%CI) for this subgroup were 4.74 (3.86-5.62), 4.39 (3.71-5.07) and 4.28 (3.94-4.62) for type 1, 2 and 3.

4.4.4 Pathogen

In 2011, poliovirus was five times isolated, in majority already described in the previous report [21]. Only one of these viruses was detected by regular surveillance activities. Isolation of a type 2 poliovirus was reported from a stool specimen from a 5-month-old boy hospitalised with gastro-enteritis which recently had been vaccinated with OPV in Curacao. The virus was characterised as polio 2 vaccine virus within 24 hrs by WHO recommended procedures with two mutations in the VP1 gene (so no VDPV).
Two polioviruses showed up in 2012 in a diagnostic laboratory during retrospective molecular typing of enteroviruses from recent years, one polio 2 virus from the stool of a four month old girl hospitalised in February 2010; and one polio 3 virus from the stool of a four months old girl hospitalised in January 2011. None of the two children had neurological symptoms; no recent travel history was recorded. RNA of both viruses was sent to the National Polio Laboratory for further characterisation: sequencing of a limited part of the VP1 gene (330 bases) showed 0 and 2 mutations when compared with the prototype vaccine strains. Original stools or cell culture material, necessary for sequencing of the complete VP1 gene, were not available anymore.
Two polioviruses were reported from research activities in two different university virology laboratories: one polio 3 vaccine strain by screening of a historic stool collection from Bangladesh, and one polio 1 vaccine strain from a Rhinovirus type 1 preparation obtained from a renowned strain library [68]. 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 10 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 2 or more cases of acute flaccid paralysis, and as ambiguous or a-VDPVs in all other cases (f.i. when isolated form sewage).

Table 7 Circulating vaccine-derived Poliovirus, 2000-2012 (WHO, data in WHO/HQ as of 28 August 2012).

country	**cVDPV type 1**													**Most recent case**
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	
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	**cVDPV type 2**													**Most recent case**
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	
Nigeria						3	22	71	66	154	27	34	1	8 Apr '12
Yemen												9		05 Oct '11
Somalia									1	6	1	9		10 Dec '11
Afghanistan											5	1		20 Jan '11
Chad											1			10 Nov '10
DR Congo									13	5	18	11	17	4 Apr '12
Niger							2			2	1	1		11 Nov '11
India										15	2			18 Jan '10
Ethiopia									3	1				16 Feb '09
Madagascar		1	4			3								13 Jul '05
country	**cVDPV 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

One study compared a fractional inactivated poliovirus vaccine (IPV) dose administered intradermally to a full dose administered intramuscularly [69]. Primary series and booster vaccination of a fractional IPV dose administered by the intradermally route was highly immunogenic and well tolerated. These data confirm the medical validity of using fractional intradermally doses of IPV. The programmatic feasibility of implementing affordable mass vaccination programmes based on this delivery mode has yet to be established.
Another study evaluated three formulations of a combined, candidate hexavalent DTPw-HBV-IPV/Hib differing only in IPV antigen content when administered to healthy toddlers [70]. The safety profile of these three formulations resembled licensed DTPW-HBV/Hib and IPV in terms of the frequency and intensity of adverse reactions after vaccination.

4.4.6 Current/ongoing research

RIVM participates in a project, sponsored by the Bill and Melinda Gates Foundation, on the in vivo effect of the poliovirus-specific antiviral drug V-073, on the duration and the extent of virus excretion.
In a double blind, placebo controlled Phase 2 experiment, 144 Swedish adults are challenged with monovalent type 1 OPV in the presence or absence of various regimes of drug administration.
RIVM was invited by the Task Force on Global Health to join the project because of earlier experience in large-scale vaccine trials (Oman study on intradermal administration of IPV, Egypt study on administration of mOPV1 to newborns) and with immunological diagnostic tests (Serum Neutralisation, IgM, IgA in various settings). The Task Force co-ordinates for WHO activities on polio antivirals from various research groups from private and public organisations.
First programmatic results of the project, for which more than 3000 stools have to be analysed by cell culture and PCR and more than 500 sera have to be tested for neutralising antibodies, as well as poliovirus type-specific IgA can be expected early 2013.

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 reintroduction of the virus. In another project, following the demonstration of a proof of principle in the 1990s [71] and responding to WHO's call for new polio vaccines [72, 73], RIVM (former parts of the NVI) continued the development of a Sabin-IPV (Inactivated Poliovirus Vaccine, based on attenuated 'Sabin' polio virus strains). This Sabin-IPV project started in 2008 and is supported by WHO using funds provided by a grant from the Bill and Melinda Gates Foundation.
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, 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 [74, 75]. Recently, Master- and Working virus seedlots (for technology transfer purposes) and clinical trial material (for phase I & phase II studies) have been produced under cGMP conditions on industrial scale. Currently, a phase II clinical trial assessing the safety and non-inferiority immunogenicity in infants in Poland is ongoing [76]. Before that time, safety and preliminary immunogenicity in adults have been demonstrated in a phase I clinical study in 2011. A comparable study in adults started in 2012, in Cuba.
The developed technology is planned to be transferred to local vaccine manufacturers in low and middle–income countries. The transfer of technology at the first individual manufacturer site (Panacea, India) was started in 2012. In collaboration with WHO, three other potential partners from South Korea, China and India were selected. Future partners will receive the existing Sabin-IPV production process and related QC testing and are encouraged to participate in further optimisation of the actual process in order to make the vaccine more affordable.

4.4.7 International developments

Now global polio eradication is near, WHO has formulated new thoughts on the past polio endgame strategy. Stopping OPV vaccination will eliminate vaccine-

associated paralytic polio (VAPP) cases immediately and stop generation of new VDPVs.
A solution for routine immunisation with IPV is within reach: intradermal administration of Sabin strain based IPV doses, with 1/5 of the amount of antigen provides a low cost and production-safe alternative for the regular IPV administration [69]. Chronic shedding of iVDPV viruses will be addressed with a cocktail of two antiviral drugs to prevent emergence of resistence.
A gradual phasing out of OPV is also a possibility. Use of bivalent OPV (as wild polio 2 is already eradicated) and later on monovalent type 1 OPV could prevent generation of new type 2 and type 3 VDPVs at an earlier stage already. Population immunity against type 2 (and later also against type 3) should be maintained high by routine IPV administration. In the end, use of any OPV will be stopped and only IPV will be used, except in polio emergencies, where mOPV will be the vaccine of choice. Pros and cons of all possible strategies are discussed in public at the moment.
RIVM participates in various research projects (see section 4.4.6) to generate scientific proof on the feasibility of these strategies.

4.5 *Haemophilus influenzae* serotype b (Hib) disease

T.M. van 't Klooster, M.J. Knol, H.E. de Melker, P. Kaaijk, N.Y. Rots, J.M. Kemmeren, A. van der Ende, G.A.M. Berbers

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 2011 and 2012 in the Netherlands.
- Low antibody levels after the primary series, as found in PIENTER 2, have been confirmed in the PIM study.

4.5.2 Changes in vaccine 2011-2012-2013

No changes in the *Haemophilus influenzae* serotype b (Hib) containing vaccines used, were implemented during 2012. See section 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 244 cases in 1993 to 12 cases in 1999 (Figure 6, Figure 7). However, in 2002-2005 the number of patients with Hib disease increased significantly, with a peak of 48 cases in 2004. Since then, the annual number of cases has decreased again to approximately 26 cases annually, with only a small increase in 2010 to 37 cases (Figure 6). In 2011 and in 2012 until July, the number of cases amounted to 22 and 18 respectively. The reason for the upsurge in cases of invasive Hib disease in 2002-2005 has remained enigmatic.

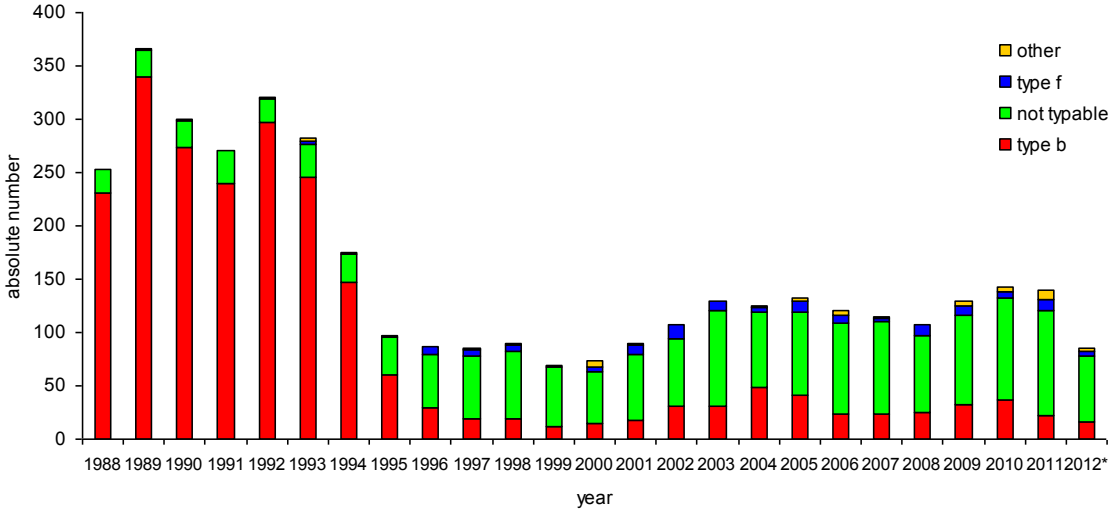


*Figure 6 Absolute number of H. influenzae isolates by serotype, 1988-2012. *Until July.*

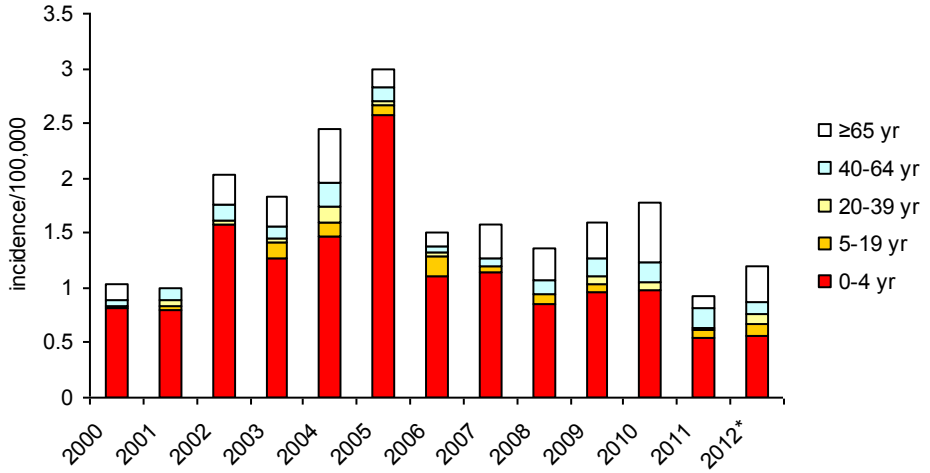


*Figure 7 Age-specific incidences of patients with invasive Hib disease, 2000-2012. *Until July.*

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 8: the annual incidence per 100,000 is shown in Figure 7).

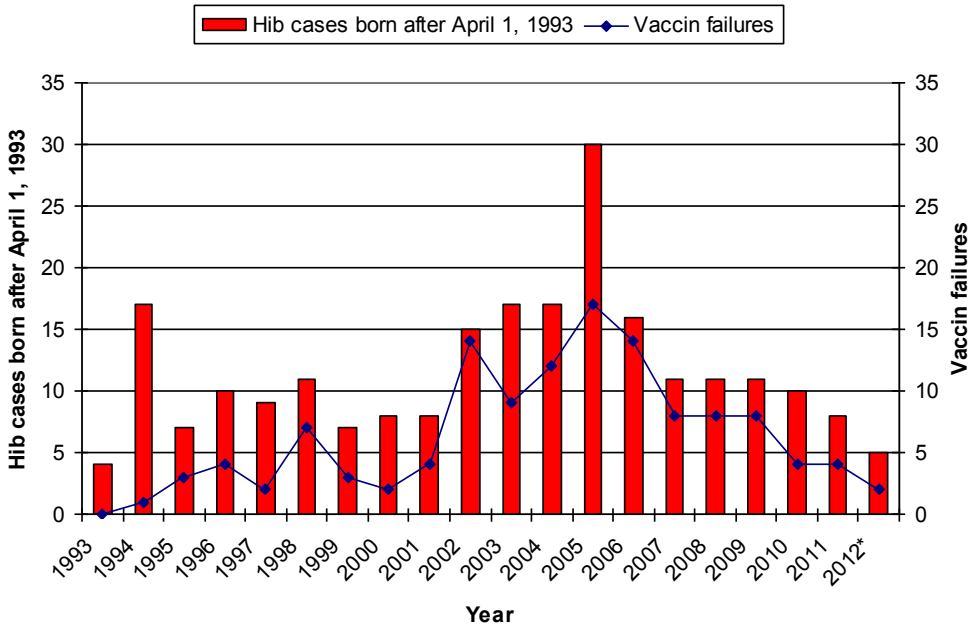


*Figure 8 Annual number of Hib infections in persons eligible for vaccination (i.e., born after 1 April 1993) and the number of vaccine failures. *Until Octobre*

4.5.4 *Pathogen*

There are no indications the pathogenicity of Hib has changed.

4.5.5 *Adverse events*

See section 4.1.5 and 4.2.5.

4.5.6 *Current/ongoing research*

The reduced vaccine-induced immunity after the primary series between 5 and 11 months of age, assessed in a large sero epidemiology survey (PIENTER 2) performed in 2006-2007, needs to be closely monitored. In the PIM-study (pneumococcal vaccination trial in 400 children), we could confirm the low antibody levels after the primary series. In line with other studies (PIENTER 1 and 2, aKwKstudy), the anti-Hib antibody levels after the booster dose at 11 months were satisfactorily [77].
Collection and typing of *H. influenzae* will be ongoing to monitor possible changes in the pathogen population.

4.5.7 *International developments*

In addition to the recently licensed Hib-MenC conjugate vaccine (Menitorix, GSK) this year, a Hib-MenCY conjugate combination vaccine (MenHibrix; GSK) has also been approved by the FDA for marketing in the US. Both vaccines are currently not licensed in Europe. MenHibrix is indicated for active immunisation to prevent invasive disease caused by *Neisseria meningitidis* serogroups C and Y and *Haemophilus influenzae* type b for children 6 weeks of age through 18 months of age.

4.6 Mumps

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

4.6.1 Key points

- The mumps outbreak which started among students late 2009 continued in 2010, 2011 and 2012. It is dominated by genotype G5 mumps virus.
- The number of reported cases in the season 2011-2012 was lower than in the previous season. The majority of cases (72%) was fully (2xMMR vaccinated.
- Sero-epidemiological results from the PIENTER 2 study (2006/7) showed a susceptible group in the low vaccine coverage areas and waning immunity after both the first and second MMR.

4.6.2 Changes in vaccine 2011-2012-2013

No changes have occurred in the MMR vaccine used in the NIP during 2011-2012. MMR vaccine is offered within the NIP to all children at 14 months and 9 years of age.

4.6.3 Epidemiology

The genotype G mumps outbreak which started among students late 2009 continued into 2010, 2011 and 2012 (Figure 9). The number of reported cases in the 2010-2011 mumps season (689) was higher than the seasons before (2009-2010: 359 cases) and after (2011-2012: 509 cases). Relatively many cases occurred outside of university cities during 2010-2011 (Figure 10). Of all cases, 58.9% was male, the median age was 22 years (range 0-86 years). The age distribution and vaccination status of cases is displayed in Figure 11. Of all cases, 72% was fully vaccinated (at least two doses of MMR).
In total 29 cases were admitted to hospital; no one died. For 126 cases (8.1%), a complication was reported (Table 8). Since the beginning of the outbreak (1/9/2012) up to week 38 in 2012, three cases of mumps related permanent deafness have been reported. Two of these have been described in recent publications [78, 79].

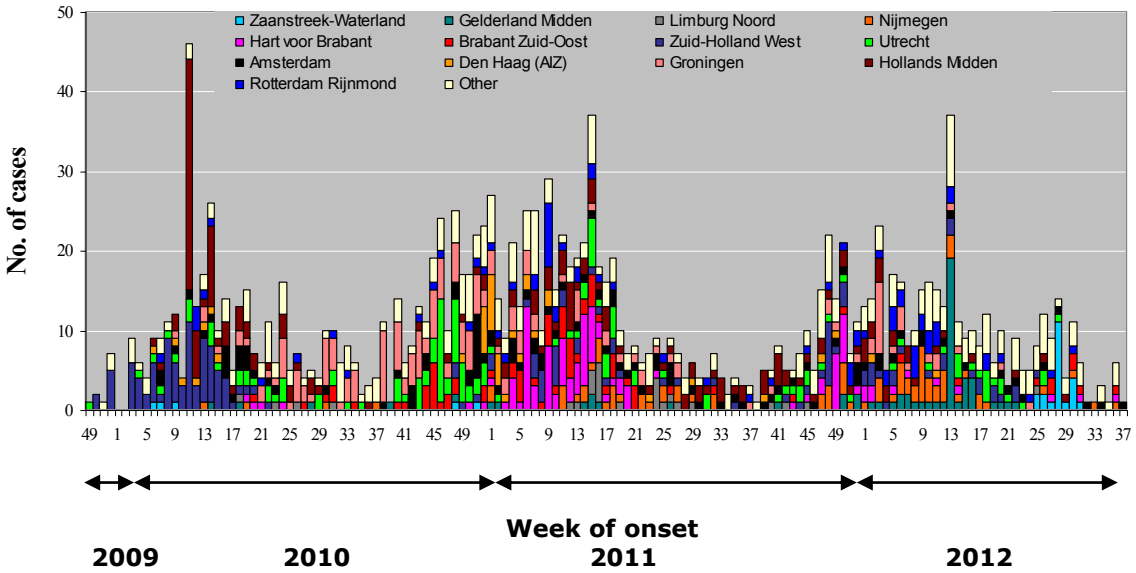


Figure 9 Number of notified mumps cases by week of onset and GGD, 1/12/2009 – 18/09/2012 (N=1552).

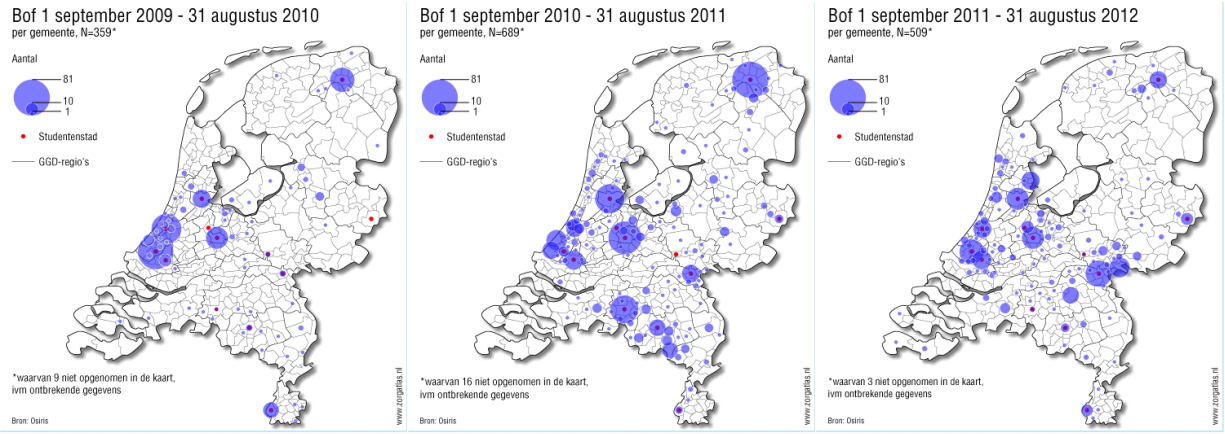


Figure 10 Number of notified mumps cases by municipality for the most recent three mumps seasons (01/09/2009-31/08/2010, 01/09/2010-31/08/2011, 01/09/2011-31/08/2012).

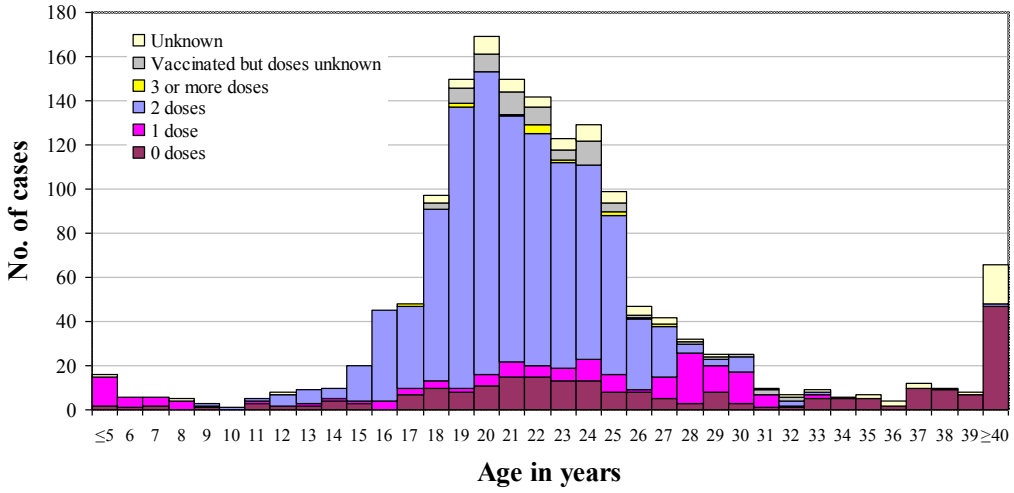


Figure 11 Number of notified mumps cases by age and vaccination status, 1/12/2009- 18/09/2012 (N=1552).

Table 8 Reported complications among cases of mumps notified between 1/12/2009 and 18/09/2012.

Complications	**n**	**% of reported cases (N=1552)**
Orchitis	106	11.6% of men
Meningitis	1	0.07
Orchitis & Meningitis	4	0.4% of men
Encephalitis	0	0.00
Pancreatitis	2	0.13
Thyreoiditis	1	0.07
Deafness	3	0.20
Meningitis, Encephalitits & Pancreatitis	1	0.07
Other	8	0.52

4.6.4 *Pathogen*

In 2011, the RIVM-LIS carried out diagnostic laboratory investigations for 1419 clinical specimens from a total of 980 suspected cases; 715 cases of these specimens were submitted by peripheral laboratories and 265 cases of the specimens were directly obtained from patients through general practitioners and health care workers from public health services. Of these, 318 cases (32%) were laboratory confirmed, mainly on the basis of a positive virus detection by real time PCR (urine, throat swab, oral fluid). Twenty-six patients were serologically tested for mumps-specific IgM antibodies while 2 of them were serologically confirmed. Mumps genotyping was performed by direct sequencing on most of the PCR positive specimens in 2011 (SH-gene region), which demonstrated the continuation of the circulation of genotype G5, though with a slightly drifted genetic profile compared to 2010.
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 is introduced in Groningen; this variant is the primary sequence type detected in most cases reported in 2011 with a number of genetic sub-variants. Few other genotype G viruses were detected in 2011, which were genetically different and one genotype D virus. These distinctive viruses were derived mostly from cases which had no direct connection with the student population. No reports of secondary mumps cases were associated with these isolated cases.

4.6.5 *Adverse events*

See section 4.7.5.

4.6.6 *Current/ongoing research*

The genotype D mumps outbreak which occurred in low vaccination coverage areas in 2007-2009 was an opportunity to study vaccine effectiveness (VE) and transmission of mumps virus to and from mumps-vaccinated individuals to close contacts with the help of oral fluid sampling to measure mumps IgG antibodies as a marker for recent mumps infection [80, 81]. Results indicate the VE against this mumps virus in the studied population (primary school children) was high (92% [95% CI 83-96%] for one dose, and 93% [85-97%] for two doses of mumps vaccine). Lower results were found when restricting the analyses to individuals with a defined exposure (in households) (VE 67% [65-95%]). This suggests the high VE estimate in schoolchildren is biased by relatively more exposure in unvaccinated individuals [82].
Mumps IgG testing of oral fluids of the same primary school study population suggested the mumps virus infection attack rates were about three times higher than the attack rates based only on clinical symptoms [81]. In a different study, the risks of vaccinated individuals to infect close contacts were considered low [80]. It is uncertain whether these results obtained during a genotype D outbreak in a primary school aged population can be extrapolated to the current genotype G outbreak among young adults.
In May 2011, ZonMW funded a mumps study which incorporates three objectives (work packages) as the direct consequence of the advice of the outbreak management team (OMT; January 31, 2011) to initiate research to gain insight into the causal factors of the mumps outbreaks in vaccinated persons and to better understand the burden of disease. The objectives are to assess 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 completed in the beginning of 2013.
Results of the PIENTER 2 study into the sero-epidemiology of mumps in the Netherlands (2006/7) indicate birth cohorts who have experienced mumps virus infection in the past have higher mumps specific IgG titers than those who have been vaccinated. A susceptible group of children was identified in the low vaccine coverage areas. In this community an outbreak of mumps occurred in 2007-2009 [83]. Waning immunity was observed after both the first and second MMR vaccination. However, after the second MMR the antibody concentration remained stable after about three till four years after vaccination.

4.6.7 International developments

Recently, a paper was published summarising the seroepidemiology of mumps in eighteen European countries as part of the ESEN-2 project [84]. The Netherlands were not included. Mean mumps IgG titers were lower in countries which had mumps outbreaks. MMR-1 coverage and an interval of 4-8 years between the two MMR doses were associated with relatively more seroprotection.

4.7 Measles

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

4.7.1 Key points

- Fifty measles cases were reported in total in 2011 of whom 34 were non-imported. The incidence of non-imported measles cases was 2,0/1.000.000, which is above the WHO elimination target (1 per million).
- Epidemiological and molecular investigation indicate that at least two third of the cases had been imported. Mostly from within Europe, either directly or as a secondary case. One larger cluster (14 cases) was associated with a school with a low vaccination coverage. About a quarter of all reported cases in 2011 was hospitalised.
- There were large outbreaks of measles in several European countries in 2011, with over 305,000 cases reported in EU/EFTA countries. The incidence is declining in 2012.
- Preparations to certify elimination of measles from the Netherlands are ongoing.

4.7.2 Changes in vaccine 2011-2012-2013

No changes have occurred in the MMR vaccine used in the NIP during 2010-2011-2012.

4.7.3 Epidemiology

In 2011, 50 measles cases were reported in Dutch citizens (3.0/1,000,000 population). An additional case was reported in a French tourist. Of the 50 infections in Dutch citizens, 34 were acquired in the Netherlands (i.e. non-imported) (incidence 2.0/1,000,000), well over the WHO target for elimination of 1/1,000,000. This is an increase compared to the fifteen cases reported in 2010 and reflects the increased transmission in other European countries (mainly France). Of the 50 cases, thirteen (26%) were hospitalised. No deaths occurred. The age of cases ranged between 0 and 42 years, the median age was 20. Of the 50 cases, 34 (68%) infections were acquired in the Netherlands and 16

(32%) abroad, most frequently (7 cases) in France. Two imported cases acquired the infection outside of Europe.
For 47 of the 50 cases the vaccination status was known. Of these, 41 (87%) were unvaccinated and six were vaccinated (two once, two twice and two unknown number of doses [85]. Of the 41 unvaccinated cases, two were below the of age of first MMR and seven were born before measles vaccination started in the Netherlands. Of the remaining 32 cases, the reason for not being vaccinated was known for 31 persons. Anthroposophic beliefs and a critical attitude towards vaccination were the most common reason for not being vaccinated (13 and 11 cases, respectively).
Among the 50 cases were 9 clusters with a median cluster size of 3. The largest cluster had 14 cases and was associated with a school with a low vaccination coverage.
Similar to poliomyelitis, efforts are ongoing to certify elimination of measles and rubella from the Netherlands, in accordance with requirements by WHO/Europe which will start in 2013. The Dutch polio certification committee has agreed to act as National Verification Commission for measles elimination. In addition, the measles elimination plan will be updated.

4.7.4 Pathogen

The measles virus genotype was determined for 28 of the 50 cases which were reported in 2011. All were of genotype D4, the most common genotype in Europe in 2011 [86].

4.7.5 Adverse events

In the Netherlands in 2011 the number of AEFI following measles, mumps and rubella (MMR) vaccination was 169, compared with 233-315 for the time-period 2005-2010 [34]. Mostly, MMR vaccination was administered simultaneously with either MenC vaccination at 14 months of age of the dT-IPV booster at 9 years of age. 48 Reports could be ascribed to the MMR vaccine. The reporting rate for 2011 is clearly lower than the last seven years, which may be caused by the transition of the surveillance system from the RIVM to Lareb on 1/1/2011. However, the total number of reported adverse events was similar, thus indicating the transition went well.
In the international literature, a case report was published about a 12-month-old infant with recurrent benign 6th nerve palsy following MMR and varicella vaccines, given on separate occasions [87]. However, limited information in the literature is available regarding the safety of a repeated dose of a live vaccine. Wilson et al. showed significantly elevated risks of primarily emergency room visits approximately one or two weeks following 12 and 18 months vaccination [88]. Future studies should examine whether these events could be predicted or prevented. In a Cochrane systematic review the authors concluded the design and reporting of safety outcomes in MMR vaccine studies, both pre-and post-marketing, are largely inadequate [89].
Several studies showed concomitant administration of MMR vaccine with other childhood vaccines like Varicella [46], PCV-7 [90], and PCV7 + hepatitis A vaccines [91] is generally well tolerated.
In a follow-up study among young adults who received MMR vaccines by aerosol or injection, Diaz-Orega et al. found no statistically significant differences in incidences of clinical adverse events between vaccinees and contacts [92].

4.7.6 Current/ongoing research

Ongoing current research regarding measles at RIVM concerns mainly the optimal age for MMR vaccination. Analyses of PIENTER 2 data suggested that

measles IgG titers in infants born to vaccinated mothers are lower than in unvaccinated mothers and the period they are protected by maternal antibodies is on average 2 months less (S. Waaijenborg, personal communication). This suggests the first MMR may need to be given at an earlier age. However, evidence from immunogenicity trials, PIENTER 2 and a recent outbreak in Canada93 suggests measles vaccination is more effective when given after 14 months of age rather than earlier.
Other recent research concerns the impact of vaccination delays when responding to a school measles outbreak [94]. Maximum intervals to starting vaccination which can avoid large outbreaks, and reduce outbreak sizes, were estimated for two different scenarios. Results suggested it is possible to reduce the number of cases during a measles outbreak in a school by applying a schoolwide vaccination strategy.

4.7.7 International developments

In 2011, over 30,000 measles cases were reported in EU and EFTA countries, about half of which were reported from France [95]. The incidence of measles declined in the beginning of 2012. WHO recently published a new Measles and Rubella Strategic Plan for 2012-2020 [96]. The goals are to reduce mortality by 95% compared to 2000 and to achieve regional measles and rubella/congenital rubella syndrome (CRS) elimination goals by 2015 and by 2020 to achieve elimination in at least five WHO regions. Five key strategies are defined:

- high vaccine coverage with 2 doses of measles and rubella containing vaccine;
- effective surveillance, monitoring and evaluation;
- outbreak preparedness and response, and case management;
- communication to build public confidence and demand for immunisation;
- research and development.

The RIVM laboratory continues to work with WHO/Europe to develop Luminex multiplex measles serology for surveillance and research purposes.

4.8 Rubella

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

4.8.1 Key points

- The rubella incidence during 2011 was very low (two cases; 0.12/million population).
- Nearly 4000 suspected rubella cases were reported in the WHO European region in 2011, mainly attributable to an outbreak in Romania.

4.8.2 Changes in vaccine 2011-2012-2013

No changes have occurred in the MMR vaccine used in the NIP during 2011-2012.

4.8.3 Epidemiology

During 2011, two cases of rubella were reported (incidence 0.12/million population). One was an unvaccinated 38-year old man who acquired the infection most likely in Tanzania. The other was a once vaccinated 50-year old woman with no known source of infection. In 2012, up to week 38, two rubella cases were reported also.

4.8.4 Pathogen

From none of the cases in 2011 or 2012 a rubella genotype could be determined.

4.8.5 Adverse events

See section 4.7.5.

4.8.6 Current/ongoing research

The results of the PIENTER 2 analyses (not yet published) suggest the Dutch population is well-protected against rubella, with exception of 0-14 month old children and children in the low vaccination coverage areas. There is evidence of waning immunity and of lower levels in vaccinated cohorts compared to birth cohorts exposed to wild type virus infection.
Novel laboratory strategies have been developed to enhance non-invasive sampling of patients (dried blood spots/saliva) and differential serological screening of cases and clustered outbreaks for measles and rubella. To this end, a multiplex IgM microarray has been developed at RIVM as a novel surveillance tool to provide rapid differential diagnosis (measles/rubella/Parvo B19) for rash illness outbreaks in collaboration with municipal health services (GGD).

4.8.7 International developments

In the WHO European Region nearly 4000 suspected rubella cases were reported in 2011 [97], mainly attributable to an outbreak in Romania.

For information on the global and regional WHO strategies for measles and rubella and the Dutch strategy and verification committee, please see Chapter 3.7 on Measles.

4.9 Meningococcal serogroup C disease

T.M. van 't Klooster, M.J. Knol, P. Kaaijk, N.Y. Rots, J.M. Kemmeren, A. van der Ende, G.A.M. Berbers

4.9.1 Key points

- The incidence of meningococcal serogroup C disease has strongly decreased since the introduction of vaccination in 2002; only three cases were reported in 2011.

4.9.2 Changes in vaccine 2011-2012-2013

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 in 2002, the incidence of Meningococcal serogroup C disease has strongly decreased (Figure 12). In 2011, only three cases of invasive meningococcal group C disease were reported. All three cases were older than 18 years (Table 9), of which one case was vaccinated (see 4.9.3.2). In 2012 up to July, no cases of MenC were reported.

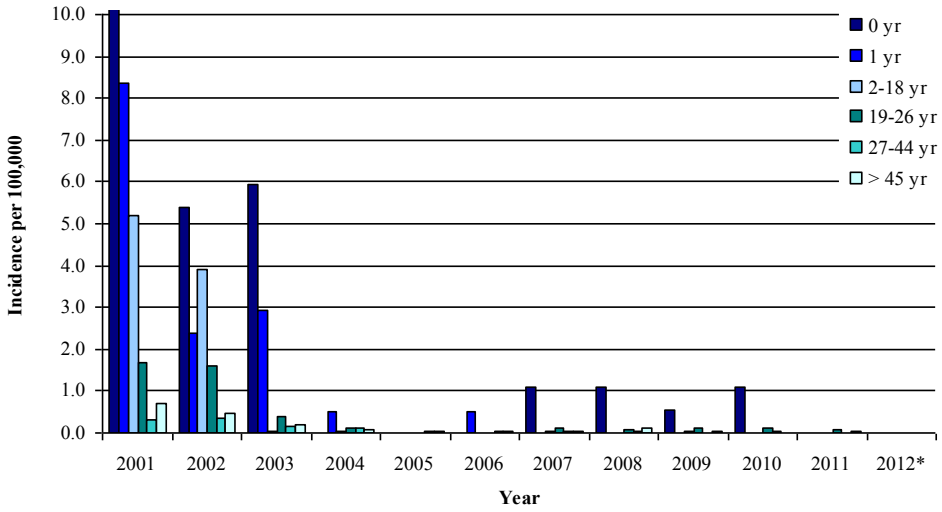


*Figure 12 Age-specific incidence of meningococcal C disease, 2001-2012. *Until July.*

Table 9 Absolute number of patients with meningococcal C disease, 2001-2012.

Age (Yrs)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012*
0	20	13	12	0	0	0	2	2	1	2	0	0
1	17	5	6	1	0	1	0	0	0	0	0	0
2-18	169	136	1	1	0	0	1	0	1	0	0	0
19-26	25	26	6	2	0	0	2	1	2	2	1	0
27-44	14	16	7	5	2	1	2	1	0	2	0	0
44-99	40	32	12	6	2	2	3	7	4	0	2	0
Total	**285**	**228**	**44**	**15**	**4**	**4**	**10**	**11**	**8**	**6**	**3**	**0**

*Until July.

4.9.3.2 Vaccine effectiveness

In 2011, one previously vaccinated case was reported. It concerned a 20-year-old female with IgA-deficiency, which might explain the vaccine faillure.

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

In the Netherlands in 2011 the number of AEFI following MenC vaccination was 86 [98]. However, MenC vaccination was mostly administered simultaneously with MMR vaccination at 14 months. Only four reports could be ascribed to the MenC vaccine.
Several trials showed a good tolerability profile of MenACWY-TT in toddlers [99], adolescents and adults [100, 101]. Two doses of the quadrivalent MenACWY-D was also safe in infants and toddlers [102] and in 2-10-year-old HIV infected children [103]. The HibMenC-TT conjugate vaccine had a similar safety profile in preterm and full-term infants [104] and can safely be coadministered with MMR and Varicella [105]. Furthermore, concomitant administration of MenACWY-CRM with MMRV vaccinations at 12 months was also well-tolerated without safety concerns [106].

4.9.6 Current/ongoing research

We evaluated the single dose MenC immunisation scheme of the Netherlands within the scope of other MenC immunisation strategies implemented in other countries [107]. Regardless of the immunisation scheme used, all countries seem to experience substantial declines in the incidence of MenC disease. Taking into account the already complex immunisation schedules of most countries with their large number of vaccinations in the first year of life, administration of MenC conjugate vaccine after the first year of life would be beneficial. An additional advantage would be a single vaccination in the second year of life. This might be sufficient for adequate protection due to a better developed immune system compared to younger infants. However, long-term protection after a single dose in the second year of life cannot be guaranteed currently. (Functional) antibody titers have been found to decrease gradually with years after vaccination [108-110]. Therefore, a good surveillance programme, as currently implemented, is necessary for timely detection of vaccine breakthroughs and outbreaks among non-vaccinees allowing an appropriate intervention, such as deciding to administer a booster vaccination.

A clinical study (TIM: Tweede Immunisatie MenC) to determine the appropriate age of a booster immunisation at (pre)adolescence has started in October 2011 and is currently ongoing.

4.9.7 International developments

At present, apart from the Netherlands, several other countries, such as Belgium, Cyprus, France, Germany, Luxembourg and Monaco have implemented a vaccination scheme with a single dose in the second year of life. However, this approach can only be justified in countries with a relatively low incidence of serogroup C meningococcal disease in the first year of life prior to introduction of the MenC vaccine. Recently, Austria and Switzerland have introduced an additional booster dose in teenagers besides the primary single dose in the second year of life. This vaccination schedule anticipates the observed waning immunity with respect to the decline in seroresponse found after one dose in the second year of life. The UK gives two vaccinations with conjugated MenC vaccine at the age of 3 and 4 months in their vaccination scheme, while a booster dose at the age of 12 months is given with Menitorix (GSK), a combination Hib-MenC conjugate vaccine (not licensed in the Netherlands). This year, also a combination Hib-MenCY (MenHibrix; GSK) has been approved by the FDA for marketing in the US.
In the US and Canada an adolescent booster with monovalent MenC or tetravalent MenACYW is now part of their immunisation programme; such a booster is advised in the UK, but not yet implemented.

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

- The incidence of notified acute HBV infections dropped to an all time low since hepatitis B could first be diagnosed (late 1960s).
- The decrease is mainly attributable to a decrease in notifications in men who have sex with men (MSM). The number of cases with no information on risk exposure also declined.

- Screening of first generation migrants for chronic hepatitis B is likely to be cost-effective. Development of a national policy in this area, also taking into account HCV, is a priority.

4.10.2 Changes in vaccine 2011-2012-2013

From birth cohort August 2011 all infants in the Netherlands are offered 4 doses of hepatitis B virus vaccination, as part of the Infanrix hexa vaccine at 2, 3, 4 and 11 months of age.

4.10.3 Epidemiology

In 2011, 1732 cases of hepatitis B virus (HBV) infection were notified. Of these, 1537 (89%) were chronic infections and 157 (9%) acute (38 cases unknown status). Compared to 2010 the number of notifications of acute HBV infection decreased by 19% (2010: 194 cases) [111]. The incidence of acute HBV notifications in 2011 was 0.9 per 100,000 population (2010: 1.2/100,000); 1.5 among men and 0.4 among women. Since 2004, the number of acute HBV notifications decreased by 47% (2004: 296 cases, 2011: 157). This decrease is mainly attributable to a decreasing number of cases reported in men who have sex with men (-51%). Among women, the incidence of acute HBV is more or less stable since the early 1990s, with a small decline since 2008 (Figure 13). In 2011, most cases of acute HBV infection (67%) were acquired through sexual contact. For 25% of reports of acute HBV infection the most likely route of transmission remained unknown, despite source tracing. Among men (122 cases), sexual contacts between MSM accounted for 39% of acute infections (n=48) and heterosexual transmission for 19%. Among women (35 cases) heterosexual contact accounted for 80% of cases.

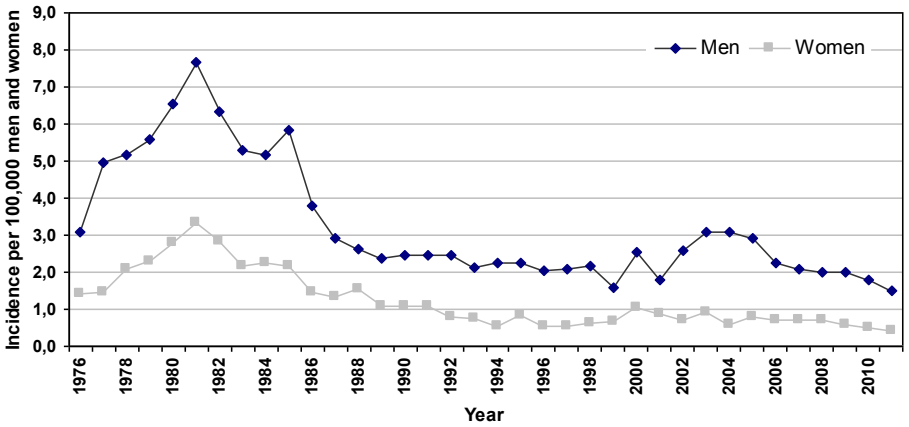


Figure 13 Incidence of notified acute HBV infections among men and women, the Netherlands, 1976-2011 (Source: Osiris/IGZ database).

A recent study from Amsterdam studied acute HBV cases excluding MSM, injecting drug users (IDUs) and children. This analysis suggests the incidence of hepatitis B is higher in both first and second generation migrants than in the indigenous Dutch population [112]. There was an increasing incidence in the Dutch/Western born population in Amsterdam since 1999 (13% increase each year) from 0.2/100,000 in 1999 to 2.1/100,000 in 2009. The authors plead for screening of first generation migrants for chronic HBV infection and catch-up vaccination for both first and second generation migrants. Regarding the latter,

several aspects would need assessment including cost-effectiveness and feasibility.
Regarding migrant screening for chronic HBV infection, several projects have been carried out in the Netherlands [113, 114]. Veldhuijzen et al. assessed the cost-effectiveness in the Netherlands of systematically screening migrants from countries which have high and intermediate HBV infection levels [115]. People with chronic hepatitis B virus (HBV) infection are at risk of developing cirrhosis and hepatocellular carcinoma. Early detection of chronic HBV infection through screening and treatment of eligible patients has the potential to prevent these sequelae. In this study, a Markov model was used to determine costs and quality-adjusted life years (QALYs) based on epidemiologic data and information about the costs of a screening programme for patients who were and were not treated. According to Veldhuijzen, a single screening for HBV infection could reduce mortality of liver-related diseases by 10%. The incremental cost-effectiveness ratio (ICER) of screening, compared with not screening, would be € 8966 per QALY gained. Systematic screening for chronic HBV infection among migrants is therefore likely to be cost-effective, even using low estimates for HBV prevalence, participation, referral and treatment compliance. Early detection and treatment of people with HBV infection can have a large impact on liver-related health outcomes. Development of a national policy on this subject is a priority.

4.10.4 Pathogen

Molecular sequencing and typing of acute HBV cases continued in 2011. We received 96 samples for genotyping. PCR amplification and sequencing gave results for 88 (56%) samples for the S-region and 91 for the C-region (58%). A minimum spanning tree on the basis of S-region sequences is given in Figure 14. This shows the largest cluster of cases is still among genotype A cases.

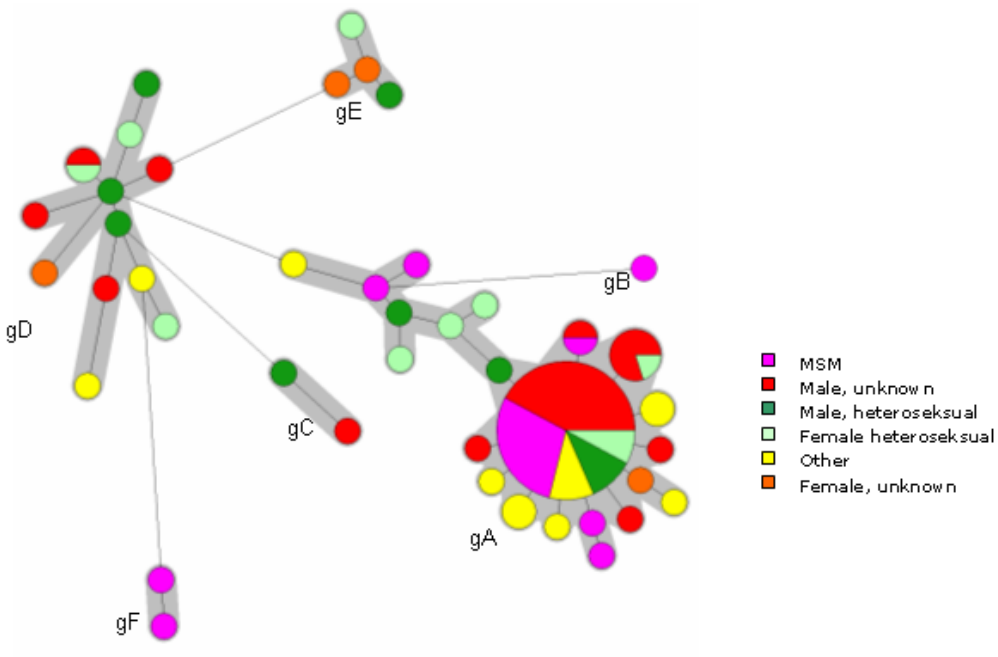


Figure 14 Minimum Spanning Tree of acute HBV cases in 2011.

4.10.5 Adverse events

In 2011, universal hepatitis B vaccination was introduced in the Netherlands for infants. This vaccine is administered in the combination vaccine DTaP-Hib-IPV-HepB and given simultaneously with pneumococcal vaccination. Therefore, the number of spontaneous reports received by Lareb can not be ascribed to the different vaccines. The number of reports received in 2011 is lower compared to earlier years, which may be caused by the transition of the surveillance system from the RIVM to Lareb at the 1/1/2011. However, the total number of reported adverse events was similar, indicating the transition went well. It seems unlikely the introduction of hepatitis B vaccination has led to more reports.
In earlier years, associations between hepatitis B vaccines and the onset of rheumatoid arthritis have been reported. However, in a large retrospective study Ray et al. did not find a statistically significant association between exposure to hepatitis B vaccine and onset of this diseas [116]. A post-marketing, double blind, randomized, controlled clinical trial assessed the safety profiles of four commercially available recombinant hepatitis B vaccines in healthy adults. It showed the four vaccines were well tolerated and poorly reactogenic. No serious adverse events were observed [117].
Four studies evaluated the safety of a novel hepatitis B vaccine with enhanced phosphate content in the aluminum adjuvant (mpHBV). All studies demonstrated the safety of this vaccine was comparable to licensed control vaccines in infants [118-120] as well as in older adults [121]. One study showed another investigational vaccine, HBsAg-1018 ISS (HBV-ISS), which was well tolerated with a safety profile similar to a licensed comparator vaccine [122]. Halperin et al. showed a rapid schedule with a 4-week interval of HBV-ISS was well-tolerated [123, 124].

4.10.6 Current/ongoing research

Molecular typing of notified acute HBV cases and of chronic HBV cases in the target groups for selective vaccination continued in 2012 and will continue in 2013. Also ongoing is the participation of the RIVM-CIb in the EU project EUHepscreen (see below).
The recent decline in notifications of acute HBV among MSM is currently being studied using a transmission model developed at the RIVM-CIb. Preliminary results indicate this decline can be attributed to the risk-group vaccination of MSM (implemented since 2002), reaching the most at risk within this group, meaning MSM engaging with many different sexual partners [125].
A related research priority is to assess the quality of access to care including treatment for chronic HBV cases, e.g. the timeliness and equity of this. A register of chronic HBV cases would be a useful framework for this type of research.
Regarding vaccination, the cost-effectiveness of catch-up vaccination for first and second generation migrants (see section 4.10.3) may need assessment.

4.10.7 International developments

The EU funded project EUHepscreen which started end of 2011 continued in 2012. It aims 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 GGD Rotterdam/ErasmusMC and includes 12 European partner institutions, including RIVM. Further details can be found on www.hepscreen.eu.

4.11 Pneumococcal disease

T.M. van 't Klooster, M.J. Knol, H.E. de Melker, P. Kaaijk, N.Y. Rots, J.M. Kemmeren, A.W.M. Suijkerbuijk, A. van der Ende, G.A.M. Berbers

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 and in other age groups, including adults over 65 years of age.
- The reduction in vaccine types has been partly counterbalanced by an increase in non-vaccine type IPD. The overall incidence decreased for 0-4 year-olds, but remained more or less stable for the older agegroups.
- On basis of immunogenicity, the PIM study revealed that in the period between the primary series and the booster dose, the 2-4-6 and 3-5 PCV-schedules were superior to the (Dutch) 2-3-4 and 2-4 schedule. After the booster dose at twelve months, all four immunisation schedules showed similar and protective antibody concentrations. When opting for a reduced dose schedule, the 3-5 schedule is the best choice offering a high level of seroprotection against pneumococci.

4.11.2 Changes in vaccine 2011-2012-2013

Children born after 1st March 2011 in the Netherlands receive a 10-valent vaccine (Synflorix, GSK) instead of the 7-valent vaccine (Prevenar, Pfizer).

4.11.3 Epidemiology

4.11.3.1 Disease

Since December 2008, IPD has become a notifiable disease for children up to five 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).

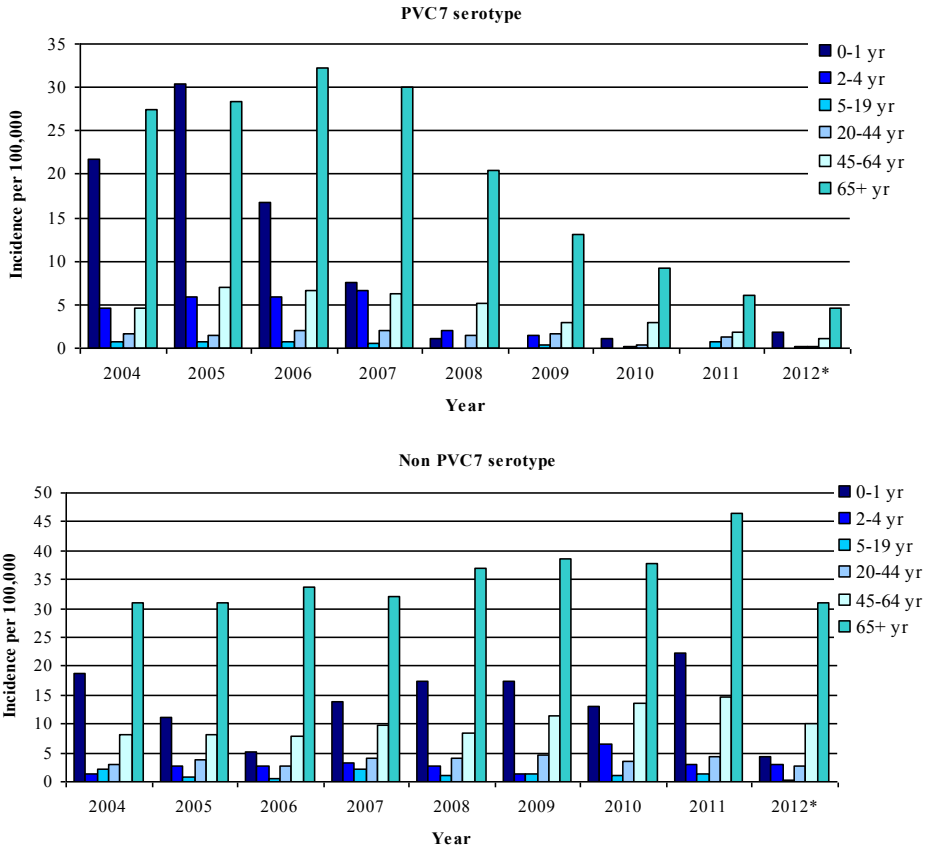


Figure 15 Age-specific incidence of 7-valent vaccine type IPD (upper figure) and non-7-valent-vaccine type IPD (lower figure).
*Incidences are calculated on cases reported by the nine sentinel labs, but extrapolated for the whole population. *Until July.*

Vaccine-type IPD decreased strongly in children < 2 years of age. A reduction of vaccine type IPD has also been observed in other age groups (Figure 15 upper). However, this reduction has been partly counterbalanced by an increase in non-vaccine type IPD (Figure 15 lower and Figure 16). The overall incidence in IPD in the 0-1 and 2-4 yrs age groups decreased; in the older age groups the overall incidence remained more or less stable.

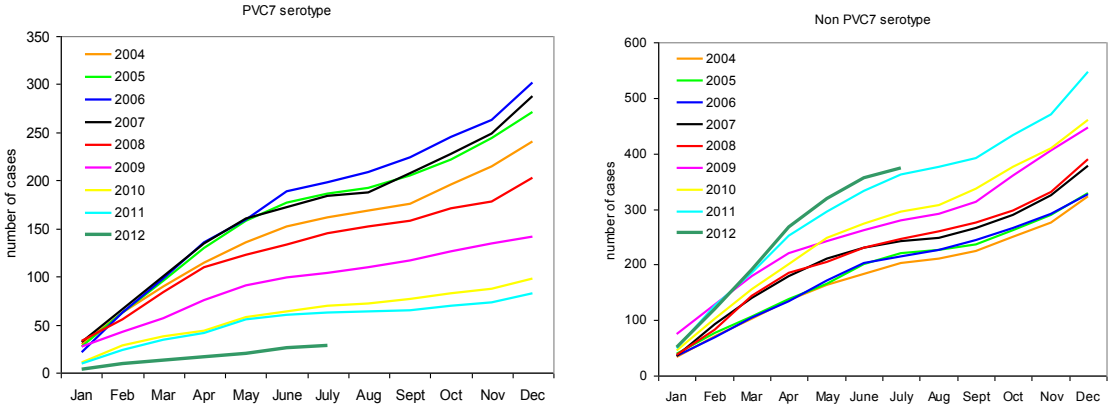


Figure 16 Cumulative number of 7-valent vaccine type IPD (left) and non-7-valent-vaccine type IPD (right) per year in patients older than 2 years of age.

Based on discharge diagnoses as registered in the National Medical Register (LMR), 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 2011. This is mainly due to an increase in the number of hospitalisations because of sepsis in persons aged 65 and older. This increase in persons aged 65 and older was also observed in the laboratory data of 2011 in the non-7-valent-vaccine types, which decreased again in 2012. The increased incidence of hospitalisation due to pneumoniae in children younger than 3 months and 6-11 months old in 2010 has decreased again in 2011 (Figure 17).

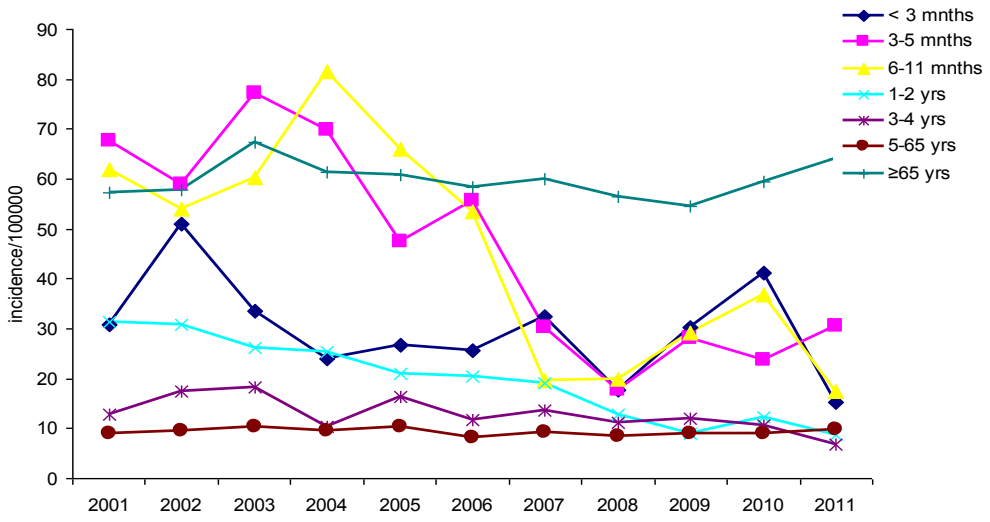


Figure 17 Age-specific incidence of hospitalisation due to pneumococcal disease (i.e. ICD9 codes 3201 (pneumococcal meningitis), 0382 (pneumococcal septicemiae), 481 (pneumococcal pneumoniae) and 4823 (pneumoniae by Streptococcus).

4.11.3.2 Vaccine effectiveness

Up to July 2012, ten vaccinated children have been reported with vaccine type IPD (Table 10).

Table 10 Vaccinated children which 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	-
2012	45	19F	4	-
2012	63	18C	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

In the Netherlands in 2011, the number of AEFI following pneumococcal vaccination was 521 [34]. In the first two months of 2011, PCV7 was included in the NIP, resulting in 298 reports. In March 2011, PCV10 was introduced, resulting in 223 reports for the rest of the year. So it seems PCV10 has a more favourable safety profile compared to PCV7. However, pneumococcal vaccination was mostly administered simultaneously with DTaP-Hib- or DTaP-Hib-HepB vaccination in infants. Therefore, the number of spontaneous reports received by Lareb can not be ascribed to the different vaccines.
Liakou et al. demonstrated PCV7 is safe in children with idiopathic nephritic syndrome [126]. Trials conducted to assess the safety and reactogenicity of PCV10 showed a good safety profile of this vaccine when co-administered as a 3-dose primary vaccination course [127-130]. Studies conducted to compare the safety of PCV13 with PCV7 showed no differences in safety and reactogenicity profiles between these vaccines [131-133], also when administered to children who had previously received PVC7 [134, 135]. Children <5 years of age vaccinated with a 23-valent pneumococcal polysaccharide vaccine (PPV) also reported no serious adverse events (SAEs) [136].
In adults, coadministration of PCV13 and trivalent inactivated influenza vaccine was well tolerated [137]. Sanford showed adverse events (AEs) within 14 days of vaccination were mostly of mild to moderate severity, with serious events occurring in 0.2-1.4% of PCV13 and 0.4-1.7% of PPV23 recipients [138]. In a study of older adults, second and third doses of PPV23 administered ten years after first or second doses, were generally well tolerated [139].

4.11.6 Current/ongoing research

The PIM ('Pneumokokken Iets Minder') study, a large randomised controlled trial (RCT), comparing the immunogenicity of 13-valent pneumococcal conjugate vaccine (PCV13) in four internationally used immunisation schedules was conducted in the Netherlands. In total 400 healthy 'at term' born infants were randomized to receive PCV13 at 2-4-6 months (USA schedule), 3-5 months (Scandinavian schedule), 2-3-4 months (Netherlands schedule) or 2-4 months (UK schedule) with a booster dose at 11 months. All infants received DTaP-IPV-Hib vaccine at 2-3-4 and 11 months.
At 12 months of age, after the booster dose, all four immunisation schedules show adequate protection and similar antibody concentrations against the 13 vaccine serotypes and above the protective level of 0.35 µg/ml. However, in the period between the primary series and the booster dose, the 2-4-6 and 3-5 schedule are clearly better than the 2-3-4 and 2-4 schedule with respect to their induced IgG levels (Figure 18). When opting for a reduced dose schedule, the 3-5 schedule is the best choice offering a high level of seroprotection. Clinical effectiveness of the 3-5 schedule is confirmed by countries that already have implemented this schedule in their NIP. Any negative effects which the implementation of the 3-5 schedule might introduce are probably nullified by the already existing herd immunity. It is recommended to consider a reduced pneumococcal vaccination schedule in the Netherlands [77].

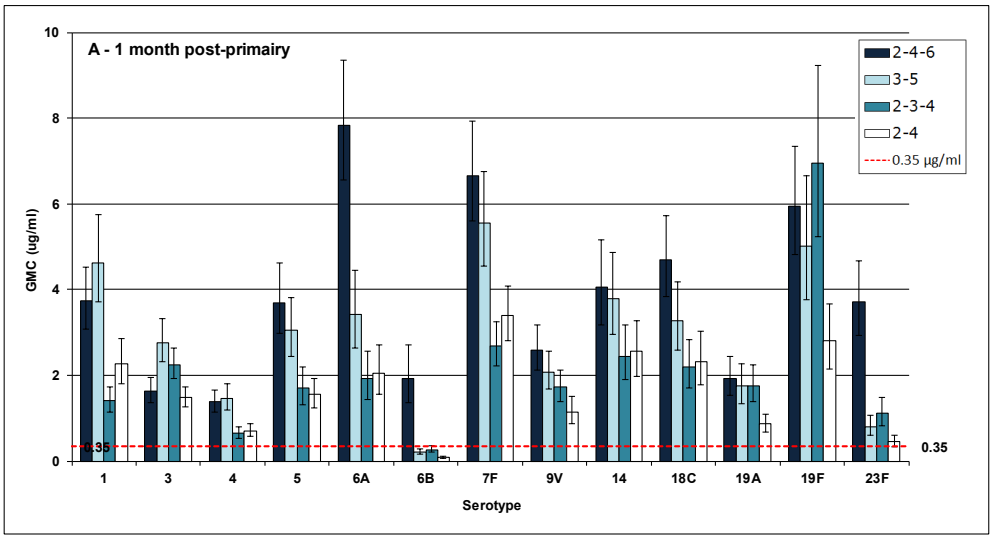


Figure 18a Pneumococcal serotype-specific antibody GMCs measured one month after the primary vaccination series.

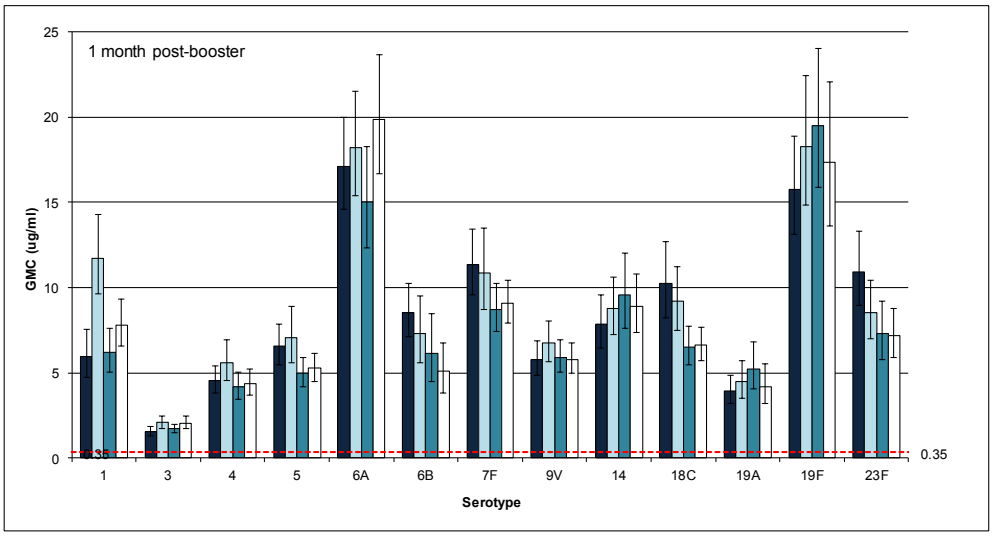


Figure 18b Pneumococcal serotype-specific antibody GMCs measured one month after the booster dose of PCV13. Note that the scale of the Y-axis differs from that of figure 18a.

Antibody levels and cellular immunity are being evaluated in the PIEN study, in blood samples collected at different time points from children vaccinated with PCV10 or PCV13. PCV10 is the current pneumococcal vaccine in the NIP and the group vaccinated with PCV13 is included to bridge the serological data with the PIM study. 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 in infants and their parents. Currently a study is being performed evaluating pneumococcal carriage 6.5 years after introduction of PCV7. 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 (see section 4.11.3.1).

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. In collaboration with Sanofi NVI/RIVM has 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.
Immunisation of mice with both monovalent PLYD1 and a trivalent formulation containing PLYD1 elicited protective immune responses after challenge with *S. pneumoniae*.

4.11.7 International developments

Merck has performed additional preclinical studies in rabbits with their 15-valent pneumococcal conjugate vaccine in addition to their studies in infant rhesus monkeys. They have not started any clinical trials yet. The vaccine adds serotype 22F and 33F to the serotypes covered by Prevnar 13. GSK has started a clinical study in Gambia to increase the coverage of Synflorix by adding several pneumococcal proteins to the conjugates.
Sanofi/Intercell and GSK have a clinical programme running with a combination of several protein vaccine candidates. Sanofi is testing a trivalent protein vaccine (PlyD1, PhtD and PcpA) and GSK is testing a bivalent vaccine (dPly, PhtD). These proteins will induce immune responses which are not serotype specific and thereby increasing the possible coverage of pneumococcal vaccines. The protein vaccines have shown to be safe and immunogenic in adults. GSK has also shown their vaccine is safe and immunogenic in toddlers [140].

4.11.7.1 Cost-effectiveness

Earnshaw et al. examined public health and economic impacts of the 10-valent (PCV10) and 13-valent pneumococcal conjugate vaccine (PCV13) for the paediatric national immunisation programme in Canada [141]. PCV13 offers broader protection against *S. pneumonia.* However, PCV10 offers potential protection against non-typeable *Haemophilus influenzae*, due to the carrier protein incorporated. Following the decision-analytic model, PCV13 was estimated to prevent more cases of disease than PCV10. Considering the epidemiology of pneumococcal disease in Canada, PCV13 has shown to be a cost-saving immunisation programme because it provides substantial public health and economic benefits compared to PCV10.
Kuhlmann et al. estimated the potential cost-effectiveness and benefit-cost ratios of the adult vaccination programme (18 years and older), considering the launch of the pneumococcal conjugate vaccine for adults (PCV13) in Germany [142]. In Germany, pneumococcal polysaccharide vaccination (PPV23) is recommended for all persons >60 years and for defined risk groups (age 5–59). Using a Markov model, the outcomes of PCV13, PPV23 vaccination strategies and 'no vaccination' were evaluated. A vaccination programme with PCV13 revealed the potential to avoid a greater number of yearly cases and deaths in IPD and pneumonia in Germany compared to PPV23. For PCV13, monetary savings resulting from reduction in the use of health care services compensated the extra vaccine costs. In conclusion, immunising adults with PCV13 would be economically more attractive than with PPV23.

4.12 Human papillomavirus (HPV) infection

M. Mollers, T.M. van 't Klooster, H.J. Boot†, A.J. King, M.A. Vink, M. Scherpenisse, S.H. Mooij, W. Luytjes, J.M. Kemmeren, F.R.M. van der Klis, E.A. van Lier, H.J. Vriend, A.W.M. Suijkerbuijk, J.A. Bogaards, H.E. de Melker

4.12.1 Key points

- Numbers of HPV-associated cancers have slightly increased in the last decade in the Netherlands.
- In 2011, the reporting rate of adverse events was lower than in 2010.
- In a study comparing characteristics of vaccinated and unvaccinated girls, it seems that routine HPV vaccination could reduce the inequity of prevention of cervical cancer.
- Prevaccination data shows that the prevalence of HPV infection varies depending on the study population. The HPV prevalence amounted to 4.4% (highrisk HPV 2.7%) in girls aged 14-16 years in the general population to 72% (highrisk HPV 58%) in a high risk population (STI clinic, PASSYON study).
- After the current vaccines which protect against 2 and 4 HPV-types and generate some crossprotection, currently new vaccines are developed which potentially give broader protection.

4.12.2 Changes in 2011-2012-2013

As a result of a European tender to purchase HPV-vaccine, the bivalent vaccine (Cervarix) is used in the Netherlands.

4.12.3 Epidemiology

4.12.3.1 HPV associated cancers

Apart from cervical cancer, HPV is also related to vaginal, vulvar, penile, anal, mouth/oral and oropharygeal cancer. The incidence of cases and deaths due to these cancers are presented in Table 11 and Table 12. 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, 40-64% of oropharyngeal cancers, and at least 3% of oral cancers [143] Recently, HPV-associated cancers have been increasing (see also section 4.12.6 international developments).

Table 11 Incidence / 100,000 (standardised by the European standardised rate) of new cervical, ano-genital, mouth/oral and pharynx/pharyngeal cancer cases in the Netherlands from 2000-2010, by cancer type (The Netherlands Cancer Registry (NKR)).

Cancer type		**'00**	**'01**	**'02**	**'03**	**'04**	**'05**	**'06**	**'07**	**'08**	**'09**	**'10**
Cervix		7,48	6,55	7,07	6,47	7,51	7,29	7,35	7,97	7,61	7,66	7,70
Ano-genital	-Vulva/vagina	2,52	2,60	2,57	2,82	2,74	2,74	2,9	3,31	3,04	3,49	3,43
	- Penis	0,97	1,18	1,27	1,23	1,39	1,24	1,31	1,23	1,39	1,46	1,43
	- Anus	0,64	0,69	0,61	0,73	0,57	0,70	0,80	0,72	0,80	0,80	0,83
Mouth		4,47	4,51	4,43	4,83	4,78	4,95	4,64	4,59	4,72	4,87	5,05
Pharynx		3,13	3,12	3,09	3,09	3,20	3,01	3,09	2,99	3,40	3,37	3,14

Table 12 Incidence / 100,000 of deaths related to cervical, ano-genital, mouth, oropharynx and pharynx cancer cases in the Netherlands from 2000-2011, by cancer type (CBS).

Cancer type	'00	'01	'02	'03	'04	'05	'06	'07	'08	'09	'10	'11
Cervix (C53)	3.22	3.01	2.30	2.62	2.47	2.85	2.59	2.47	2.94	2.51	2.45	2.25
Ano-genital - Vulva/vagina (C51-52)	1.35	1.25	1.36	1.44	1.19	1.29	1.38	1.22	1.42	1.54	1.65	1.93
Ano-genital - Penis (C60)	0.25	0.29	0.16	0.25	0.29	0.26	0.17	0.38	0.32	0.29	0.40	0.40
Ano-genital - Anus (C21)	0.16	0.21	0.20	0.14	0.15	0.23	0.16	0.16	0.20	0.24	0.25	0.23
Mouth (C01-06)	1.41	1.35	1.29	1.57	1.46	1.44	1.41	1.46	1.43	1.63	1.67	1.63
Oropharynx (C09-10)	0.56	0.59	0.63	0.68	0.68	0.53	0.59	0.57	0.57	0.63	0.72	0.78
Pharynx (C09-14)*	1.54	1.58	1.76	1.65	1.78	1.47	1.68	1.53	1.62	1.79	1.63	1.33

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

4.12.3.2 Genital warts

Genital warts are caused by low risk HPV types 6 or 11. The number of diagnoses of genital warts reported in the national surveillance of sexually transmitted infection (STI) centre decreased from 2729 in 2010 to 2380 in 2011. The decline occurred in heterosexual men and women (-18 percent and -14 percent respectively) but among MSM there was a small increase (+1.6 percent). At GPs, the number of reported diagnoses of genital warts was estimated at 20,168 (95% CI 16,306-25,175) in 2010 (55% men and 45% women), a small decrease of 4% compared to 2009. In particular the number of diagnoses of genital warts among women decreased by 4% compared to 2009 [144].

4.12.4 Adverse events

During 2011, Lareb received 51 spontaneous reports of AEs following vaccination against HPV. Five of them were severe reactions [145]. The reporting rate for 2011 is clearly lower compared to the reporting rate of 2010 (n=129), which partly may be caused by the transition of the surveillance system from the RIVM to Lareb at the 1/1/2011. However, it may also be a result of a declining reporting behaviour resulting in an increased underreporting. Furthermore, in 2011 there was no media attention and rumour compared to earlier years which also may have played a role.
Several studies assessed the safety of the bivalent HPV (HPV2) vaccine. Three studies demonstrated a good safety profile in adolescent girls [146] and women aged 15-25 years [147]. Concomitant administration of HPV2 vaccine with Tdap and/or MenACWY in different regimens also showed an acceptable safety profile [148].
Other studies assessed the safety of the quadrivalent HPV (HPV4) vaccine. In a study of over 600,000 HPV4 vaccine doses administered, no statistically significant increased risk for any of pre-specified adverse events after vaccination was detected [149]. In an observational study, no autoimmune safety signal was found in women vaccinated with HPV4 [150]. In a trial among 9-15 year old Chinese male and 9-45 year old Chinese females, Li et al. found HPV4 was generally well tolerated, with no vaccine-related serious adverse events [151]. HPV4 vaccine also demonstrated to be well tolerated in patients with stable SLE [152]. In an observer-blind study, Einstein et al. found both HPV2 and HPV4 were generally well tolerated [153]. Not only in women, but also in men aged 16-26 years, HPV4 vaccine had a favourable safety profile [154].

4.12.5 Current/Ongoing research

4.12.5.1 HPV-DNA

HPV prevalence among young girls (HAVANA study)
A five-year prospective cohort study, which was initiated in 2009 among 14- to 16–year-old vaccinated and unvaccinated girls, is still ongoing. The primary aim is to monitor the effect of vaccination on HPV-type distribution amongst these two groups. Therefore, vaginal selfswabs collected in this cohort were tested for the presence of HPV DNA. In this study, 1800 girls participated at baseline, 1503 in the first year and 1360 in the second year of follow up. The hrHPV prevalence rises from 2.7% at baseline to 4.9% in the first year of follow up and to 7.2% in the second year of follow up. In coming years (round four is almost completed) the relationship between HPV DNA, antibodies (mucosal and systemic) and cellular immunity will be explored.

HPV prevalence among young STI clinic attendees (PASSYON study)
To monitor possible changes in the HPV dynamics over time in the post vaccination era compared to prevaccination era, a biennial cross-sectional study including 16- to 24-year-old male and female STI clinic attendees was set up [155]. In 2009 and 2011, the first two rounds of this study took place in 14 STI clinics throughout the Netherlands, of which 10 STI clinics participated in both rounds. The anogenital samples collected were analysed for the presence of HPV DNA and the HPV type was determined. Results of the first round showed high prevalence rates (any HPV 67%) [155]. Females had higher HPV prevalence rates than males (72% versus 54% respectively) and were more often infected with a hrHPV type. In addition, HPV16/18 was more commonly detected in females than in males (23% versus 16% respectively). HrHPV infection was especially related with high sexual risk behaviour in contrast to lrHPV types. The results of the second round (2011) showed similar prevalence rates and related behavioural factors. This study is ongoing.

HPV and viral load
To monitor the effect of HPV vaccination on (transient) HPV infections, measurement of viral load is also relevant. The HPV viral load reflects the productivity of DNA replication in the HPV lifecycle; therefore its level may play a role in defining the course of HPV infections. High HPV viral load is believed to be associated with HPV infection persistence and cervical malignancies. We aim to evaluate the effect of HPV 16/18 vaccination on the viral load of transient and persistent HPV16/18 infections in the earlier mentioned HAVANA study and CSI study. We are currently setting up HPV16 and -18 viral load assays by real time PCR, targeting the L1 gene and will use this test to assess the severity of the HPV16/18 infections in the HAVANA study. Preliminary analyses of HPV16 viral load in samples from the CSI study showed that HPV16 viral loads are higher in persistent infections compared to transient infections.

4.12.5.2 Serology

Monitoring of HPV using serology
Awaiting the primary outcome of HPV vaccination (reduction of cervical cancer and other HPV-related cancers), serology can play a role to monitor changes in HPV infection dynamics. However, in the interpretation it should be taken into account that HPV antibodies cannot be directed by correlated with protection. Furthermore, only a part of the HPV-infected individuals show a seroreponse.

Besides DNA, which is a marker for a current infection, serology can provide us with information about past exposure (although not all people with an HPV

infection seroconvert). Changes in HPV antibody seroprevalence of seven high-risk HPV types over time were evaluated among the Dutch general population in the pre-vaccination era. Serum samples of men and women (0-79 years of age) from two cross-sectional population based serosurveillance studies performed in 1995-96 (PIENTER 1, *n*=3303) and 2006-07 (PIENTER 2, *n*=6384) [156] were tested for antibodies against HPV16, 18, 31, 33, 45, 52 and 58. A higher overall seroprevalence in individuals older than 15 years of age was found for HPV16, 18, 31 and 45 in 2006-07 as compared to 1995-96. For HPV33, 52 and 58 seroprevalences were comparable over this 11-year time period. Seropositivity for one or more HPV types was significantly higher in 2006-07 (23.1%) than in 1995-96 (20.0%) (p=0.013). HPV antibody seropositivity for more than one HPV type increased from 7.1% in 1995-96 up to 10.2% in 2006-07 (p<0.0001). Differences in HPV seropositivity for at least one of the seven HPV types between both surveys could also be explained, in addition to demographic characteristics (age, sex, urbanization degree and ethnicity), by changes in sexual behaviour (marital status, age of sexual debut and ever reported a STI). Seroprevalence studies provide insight into the distribution of HPV types and infection dynamics in the general population over time, which is important to assess the impact of HPV-vaccination.

Measuring HPV-specific mucosal antibodies (HAVANA study)
The bivalent HPV16/18 vaccine induces high antibody concentrations in serum while data about antibody presence in the cervical mucosa are limited. We investigated pre- and post-vaccination antibody responses against seven high-risk HPV types (HPV16, 18, 31, 33, 45, 52 and 58) by detection of IgG and IgA HPV-specific antibodies in cervical secretion samples (CVS) and serum. From an HPV vaccine monitoring study (HAVANA study) CVS and serum samples were available (pre-vaccination (n=297), one year (n=211) and two years (n=141) post-vaccination) from girls aged 14-16 years. CVS was self-collected using a tampon. After vaccination with the bivalent HPV vaccine HPV16 and 18 IgG and IgA antibodies were detectable in CVS and these antibody concentrations correlate well with serum antibody levels. Antibody levels in CVS were lower as compared to serum; levels remained constant up to two years post-vaccination. Vaccine induced antibodies in the systemic circulation might transudate and/or exudate to the cervical mucosa although other immune mechanisms can not be excluded. These important immune mechanisms probably contribute to sufficient antibody levels at sites where HPV infections actually take place and therefore can provide protection against HPV infection and/or re-infections [157].

4.12.5.3 Vaccine uptake

Knowledge of HPV amongst vaccinated and unvaccinated girls
Online questionnaires were sent to approximately 20.000 randomly selected 16-17 year old girls, which were targeted in the catch-up vaccination campaign in 2010. Out of these girls, 2989 participated (65% vaccinated, 35% unvaccinated). Vaccinated and unvaccinated girls were similar with regard to ethnicity, education level and knowledge of HPV transmission. However, vaccinated girls had slightly more general knowledge of HPV, lived in more urbanised areas and were less likely to have a religious background. Vaccinated girls were less aware of the Cervical screening programme although they were more inclined to participate in the future. Irrespective of vaccination status, 81% of the girls knew about the causal relationship between HPV and cervical cancer, but only 20% knew about the relationship between HPV and genital warts. It seems routine HPV vaccination in the Netherlands reduces the inequity of prevention of cervical cancer. Vaccination uptake is not associated with

education and ethnicity (which are related to the cervical screening programme). In addition, vaccinated girls were slightly more sexually active indicating that the impact of vaccination is not overestimated in for example modelling studies.

4.12.5.4 Safety

Association between HPV vaccination and migraine
Currently, a study is ongoing to investigate the association between a first migraine attack and HPV vaccination. Since the introduction of HPV vaccination, the number of reports of migraine is notable. In 2009 and 2010, the RIVM received 52 reports of headache, of which 8 girls were diagnosed with migraine. Although the causal relation of the reports of migraine was assessed as improbable and there are little or no pathophysiological explanations for any relation, investigation of a possible association between HPV vaccination and migraine is necessary to maintain trust in the NIP.
A retrospective cohort study in persons 12-16 years of age was conducted for the years 2004/2005/2008 (before HPV vaccination) and 2009/2010 (after HPV vaccination campaign started). All migraine cases in these years were selected from an electronic database of medical records from Dutch General Practitioners, i.e. Integrated Primary Care Information (IPCI) database, Erasmus Medical Centre Rotterdam [158].
Figure 19 shows that the incidence of a first migraine attack for 12-16 year-old girls was higher after the start of the vaccination campaign than in the period before vaccination. However, the difference was not significant. Moreover, the post-vaccination incidence for men was also slightly higher than the pre-vaccination incidence. To investigate this signal further, a hypothesis testing self-controlled case series study will be done by linking the migraine cases to the vaccination registry (Præventis, RIVM) to determine HPV vaccination status. Furthermore, after linkage, incidences in vaccinated and non-vaccinated cases can be compared.

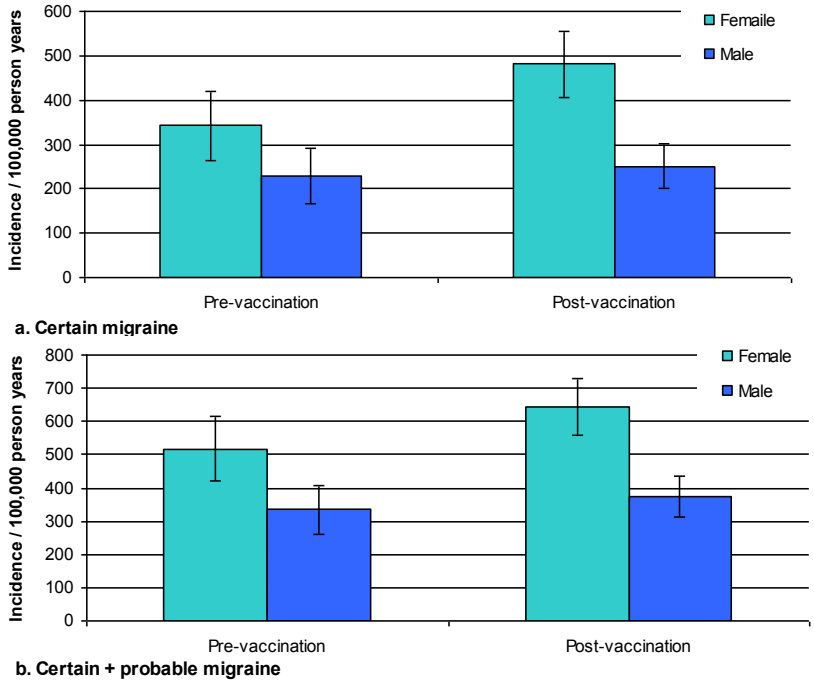


Figure 19 Pre- and post-vaccination incidences of migraine for 12-16 year-olds a. Certain migraine; b. Certain and probable migraine

4.12.5.5 Modelling

The long-term impact of female HPV vaccination in the Netherlands has been explored by mathematical modelling [159]. Underlying these projections was a type-specific transmission model [160] that had been calibrated to pre-vaccine data from a population-based study on HPV DNA testing in cervical screening. We are currently exploring the sensitivity of the modelled projections to alternative assumptions regarding the natural history of HPV infection (specifically: sex-specific differences in viral transmissibility, clearance, and natural immunity) which are in line with the pre-vaccine data. HPV DNA prevalence data among sexual health service clinic attendees provide opportunities to further test the predictions of our HPV transmission model for both sexes at relatively young age (16-24 years).
The possibility of type-replacement of HPV-16/18 by types not included in the vaccine is still an unresolved issue. Theory predicts this opportunity may arise if vaccine-type HPV interacts antagonistically with non-vaccine types, e.g. through competition for limited resources or through cross-reactive natural immunity. We are currently investigating how such conditions affect the joint prevalence of oncogenic types in endemic equilibrium, i.e. prior to introduction of the vaccine. Epidemiological studies have consistently shown that multiple-type infections occur more often than would be expected by chance, but it is unclear how this clustering of HPV types on the level of the individual can be interpreted.
As a first objective towards predicting the short-term impact of HPV vaccination, we estimated the 'waiting time' distribution from precancerous lesions (CIN2/3) to invasive cervical cancer. We developed a statistical model that uses data from Dutch national registries on the age-specific occurrence of CIN2/3 (from PALGA) and cervical cancer (from the Dutch Cancer Registry) to determine the duration between these two health states. We estimated the mean duration to be 24 years. Hence, it will take at least two decades before a reduction in the number of cervical cancer cases due to vaccination becomes apparent in the national registries. Besides, we could estimate the cumulative incidence of cervical cancer after onset of CIN2/3 for HPV-16-positive and HPV-16-negative lesions. The cumulative incidence for HPV-16-positive CIN2/3 was larger compared to HPV-16-negative CIN2/3 for the first 20 years, indicating a higher risk to progress to cancer for HPV-16-positive lesions. These findings can have important implications for the development of HPV DNA-based screening algorithms, both for vaccinated and non-vaccinated women.

4.12.5.6 Cost effectiveness

Bogaards et al. have previously shown that, in order to reduce the prevalence of HPV infection in the heterosexual population, inclusion of boys in the HPV vaccination programme is less effective than increasing the vaccine uptake among girls. However, men who have sex with men (MSM), who are at increased risk of HPV-related cancers, derive little gain from a girls-only vaccination programme and universal vaccination might still be cost-effective if the cost of vaccination is low enough. They performed a comprehensive cost-effectiveness analysis to examine the vaccine price at which male HPV vaccination can be considered 'good value for money', while accounting for the anticipated impact of female vaccination on HPV-related cancers among heterosexual men as a function of vaccine uptake among girls. At the current coverage in the Netherlands, Boogaards et al. estimate that male HPV vaccination is cost-effective at a vaccine price below € 30 per dose. However, most of the projected benefit from vaccinating boys is derived from the prevention of HPV-related head and neck cancers, for which the causal link with HPV is still uncertain. Moreover, the viability of universal vaccination depends on

numerous criteria (acceptability of male vaccination, budget impact, etc) other than the cost of vaccination [161].
In another study, Bogaards assessed the cost-effectiveness of HPV vaccination in adult women aged 17 to 25 years [162]. In the Netherlands, the use of HPV vaccines has been universally approved for women from age 12 to 25 years, but those older than 16 years receive no reimbursement for the cost of the vaccine. The calculations were based on an individual-based simulation model for cervical carcinogenesis, with HPV infection risks obtained from a type-specific HPV transmission model. The indirect protective effect from vaccinating 12 to 16 year-old girls was adjusted for and cervical screening in the model was incorporated according Dutch screening guidelines. The incremental cost-effectiveness ratio (ICER) for vaccinating 17–25 year-olds was € 22,526 per quality-adjusted life-year (QALY) at a vaccine price of € 65 per dose, a 50% reduction of the 2010 pharmacy price in the Netherlands. If cross-protection against types 31/33/45/58 was included, the ICER decreased to € 14,734 per QALY. Bogaards concludes that refunding the cost of the vaccine to 17–25 year-old women in the Netherlands can be considered cost-effective at anticipated price reductions.
According to Soergel et al., the cost-effectiveness of HPV vaccination is underestimated in many evaluations since they do not take conization-related neonatal morbidity and mortality into account [163]. Cervical intraepithelial neoplasia (CIN) represents the precursor of invasive cervical cancer and is associated with HPV infection against which two vaccines have been approved in the last years. Standard treatments of high-grade CIN are conization procedures, which are associated with an increased risk of subsequent pregnancy complications like premature delivery and possible subsequent life-long disability. HPV vaccination has therefore the potential to decrease neonatal morbidity and mortality. Soergel calculated the possible reduction rate of conizations for different vaccination strategies for Germany. Using this rate, he computed the reduction of conization-associated preterm deliveries, life-long disability and neonatal death due to prematurity and estimated the number of life-years saved and gain in QALYs. Soergel concludes the HPV 16/18 vaccines have the potential to be cost-effective regarding conization-related neonatal morbidity and mortality. This effect adds up to the reduction of cervical cancer cases and decreased costs of screening for CIN.

4.12.6 Other relevant (international) developments

4.12.6.1 Current status of HPV vaccine introduction in EU countries

A recent update report by the ECDC on the implementation of HPV in the EU shows that since 2008 HPV vaccination programmes have been implemented in most EU countries [164]. May 2012, 19 out of 29 countries in the EU (including Norway and Iceland) had implemented routine HPV vaccination programmes and 10 countries had also introduced catch-up programmes. Despite the efforts made by individual member states, coverage rates (where data are available) are lower than expected in many EU countries. In addition, target age, system of financing and delivery of the vaccines differ from one country to another.

4.12.6.2 Algorithm for screening programme cervical cancer

In 2011, the Health Council recommended the use of HPV testing in the cervical screening programme (secondary prevention of cervical cancer) in the Netherlands. Data from longitudinal research showing that hrHPV testing is more sensitive than cytology was used in this decision [165]. Also cost-effectiveness studies support the introduction of the HPV test as the primary test. Especially when the interval between screening rounds is longer [166].

HPV testing is also beneficial for the monitoring of HPV vaccination when girls who are vaccinated reach the age of screening (2028 or later).

4.12.6.3 HPV infection and associated diseases in non-cervical sites

The incidence of HPV related cancers has been increased in recent years (e.g. 2% increase in anal cancer in the general population of the USA). The efficacy of primary prevention has been shown to be high in a study of the quadrivalent HPV vaccine, in which there was a 77% reduction in incident high-grade anal intraepithelial neoplasia (HGAIN) among vaccinated HIV uninfected MSM compared with the placebo group in the per-protocol analysis and more than 90% reduction in persistent anal HPV infection with vaccine HPV types [154]. Another HPV related cancer has been identified. Beta papillomavirus (betaPV) DNA has been detected in up to 50% of cutaneous squamous cell carcinoma (SCC) of immunocompetent patients and in more than 90% of skin SCC of immunosuppressed transplant recipients, supporting the hypothesis that betaPV might play a role in the development of cutaneous SCC. This can open perspectives for clinically relevant pretransplant HPV screening and the development of preventive HPV vaccination [167].

4.12.6.4 Future HPV vaccines

Two lines of HPV vaccine development are of significance. One is the next-generation VLP vaccine developed by Merck as a replacement for Gardasil. This vaccine contains nine HPV types, adding types 31, 33, 45, 52, and 58, all oncogenic. However, it is currently unclear when this vaccine will be available and what the additional benefit will be.
The second vaccine approach under development is using the viral L2 protein instead of L1. The rationale is that the L2 protein is more conserved than L1 and the vaccine should thus be more broadly protective. Also, the vaccine is cheaper to produce, because it can be produced by bacterial expression, which is not feasible for L1 VLPs. No trial data are available yet.

5 Future NIP candidates

5.1 Rotavirus infection

I.H.M. Friesema, W. van Pelt, A. Kroneman, P. Bruijning-Verhagen, W. Luytjes, J.M. Kemmeren, A.W.M. Suijkerbuijk, H.E. de Melker

5.1.1 Key points

- After a rise in incidence of rotavirus associated gastroenteritis seen in the Netherlands in the last few years, in 2011 the incidence was lower.
- In 2011, G1[P8] was most commonly found in the Netherlands, followed by G9[P8] and G12[P8].

5.1.2 Epidemiology

The Working Group Clinical Virology reports the number of rotavirus positive results weekly (see Appendix 2). After an increase in the number of rotavirus positive samples in the past three years (2010: 2180 isolates), in 2011 this number (1504 isolates) was comparable with 2006 (1585 isolates).

5.1.3 Pathogen

The Laboratory for Infectious Diseases and Perinatal Screening (LIS) of the RIVM typed 399 rotavirus isolates received in 2011. Most isolates (92%) were from children aged 0-5 years. The most commonly found variant was G1[P8] (59%), followed by G9[P8] and G12[P8] (each 10%). The variants which were second and third in 2010, G3[P8] (25%) and G2[P4] (17%), are rarely found in 2011 with 1.5% and 3% respectively. In 6% of the isolates a mixture of G- and/or P-types was reported. Positive samples sent to the RIVM were from patients who were younger than last year with 48% being aged below 1 year in 2011 and 27% aged 1 year, a further 11% was aged 2 years, 7% was aged 3-4 years, 2% was aged 4-18 years and 4% were adults. In comparison, in 2010 17% was aged below 2 years.

5.1.4 Adverse events

RotaShield, a previous rotavirus vaccine, was withdrawn when was found after introduction that it could be associated with intussusception [168]. Since then two new rotavirus vaccines have been introduced, RotaRix and RotaTeq. Neither vaccine demonstrated an increased risk of intussusception in large international Phase III trials, but post-licensure surveillance data indicate that an increased but small risk of intussusception in the first week after administration of the first vaccine dose may exist. This association has been found in some populations [169-171] but not in others [172, 173]. Although some studies were not adequately powered to find the small increase in intussusception rate associated with vaccination [169-171], other explanations for the inconsistencies in findings could be environmental or genetic differences between study populations. In addition, the estimated baseline incidence for intussusception varies between 47/100,000 infant-years in the United States [174] to 81/100,000 in Australia [175] and 158/10,000 in Japan [176] which can substantially influence the number of vaccination related excess cases. It is therefore recommended that the baseline intussusception incidence in the Netherlands is assessed before introduction of rotavirus vaccination.

In several countries trials to assess the tolerability of rotavirus vaccines showed this vaccine is well-tolerated [177-180], even in preterm [181] or HIV-infected children [182].

5.1.5 Current/ongoing research

The LIS of the RIVM is one of the nineteen laboratories in seventeen countries participating in EuroRotaNet to monitor circulating serotypes of rotavirus in Europe. The European Rotavirus Network, EuroRotaNet, was established in January 2007. With this study the diversity of co-circulating rotavirus strains in consecutive rotavirus seasons is determined. The results for 2011 are given in section 5.1.3 Pathogen.

Recently, results of an observational study on rotavirus hospitalisations in the Netherlands were published [183]. The study was conducted among pediatric wards in three general hospitals and one pediatric tertiary care centre. Numbers of rotavirus (RV) hospitalisations were determined from five year data (2006-2010) on confirmed RV hospitalisations and adjusted for RV underreporting, assessed through active surveillance for acute gastroenteritis during the 2011 RV season. Incidence rate and RV contribution to all-cause hospitalisations was determined upon hospital administrative data and population statistics RV accounted for 6.2% (95%CI: 5.3–7.1) of all-cause pediatric hospitalisations among general hospitals and 3.1% (95%CI: 2.9–3.3) at the tertiary care centre. RV hospitalisations incidence rate in the population was 510/100,000 child-years under five (95%CI: 420-600) with an annual mean number 4800 RV hospitalisations in the Netherlands of which approximately 500 are nosocomial infections. Among general hospitals, there was a 30% increase in all-cause hospitalisations during the active season of common childhood infections compared to summer months. It was demonstrated RV is one of the main causes for seasonal peaks in all-cause pediatric hospitalisations contributing 31% to seasonal excess and representing 12.9% of hospitalisations between January and May. In addition, this study assessed potential differences in hospitalisation rates, risk of nosocomial infections, healthcare resources utilisation, complications and mortality due to RV between otherwise healthy children and children with prematurity, low birth weight and congenital pathology. All three conditions were associated with increased risks of RV hospitalisation (RR ranging from 1.6 to 4.4), nosocomial RV infection (RR ranging from 3.2-3.6), ICU admission (RR ranging from 4.2 to 7.9), prolonged hospital stay (1.5 to 3.0 excess days) and higher healthcare costs (€ 648 to € 1533 excess costs). Seven children succumbed due to RV complications, all belonging to the high-risk population. (Data not yet published)

5.1.6 International developments

In the European Union plus Iceland and Norway, eight countries have included rotavirus vaccination in the NIP (Austria, Belgium, Bulgaria, Finland, Latvia, Luxembourg, Poland, Slovenia) and the Ministery of Social Affairs of Estland recommends rotavirus vaccination without inclusion in the NIP so far [184].

Vaccination against rotavirus is mainly meant to decrease severe cases of rotavirus infections. A randomised, double-blind, placebo-controlled trial in Singapore, Hong Kong and Taiwan was extended for a third year [185]. At the start of the study, infants (6-17 weeks) had received two doses of Rotarix (RIX4414) within a time frame of 1-2 months. The efficacy against severe rotavirus gastroenteritis during the third year post-vaccination was 100% (95% CI: 67.5-100.0). The combined three-year efficacy against severe

rotavirus gastroenteritis was 96.9% (95% CI: 88.3-99.6) and 100% for G1 and 94.9% for non-G1 rotavirus types. In the United States, reductions in all-cause gastroenteritis hospitalisations and rotavirus-coded hospitalisations of 31-33% and 62-71%, respectively, were seen in the 2008 and 2009 postvaccine years compared to the prevaccine years 2000 to 2006 [186]. However, a decline was seen across all age groups in 2008, whereas the decline seen in 2009 was mainly in the vaccine-eligible age group. It is expected the hospitalisation rates among young children will continue to decrease in future years, as successive birth cohorts are vaccinated. In Belgium, the effectiveness of monovalent rotavirus vaccine was calculated over the period February 2008 – June 2010 [187]. The effectiveness on hospital admission of two doses was 90% (95% CI: 81-95%). The vaccine effectiveness against P2[P4] and G1[P8] was 85% (95% CI 64-94%) and 95% (95% CI: 78-99%) respectively.
In Spain, rotavirus is recommended but not reimbursed since end of 2006 [188]. Both Rotarix and Rotateq are available. Vaccination coverage increased from 12% in the first season to about 50% in the following years. A comparison of hospitalisations due to acute gastroenteritis and specific rotavirus gastroenteritis was made between pre and post vaccination. A decrease of 30-49% and 15-45% for overall hospitalisations and rotavirus specific hospitalisations respectively, was reported in the two years after vaccination. Overall vaccine coverage in Hungary between 2007 and 2010 was 4% to 18% [189]. In the period 2007-2011 they saw mainly G1P[8] (45%), followed by G4P[8] (23%) and G2P[4] (15%). Brazilian children are vaccinated with a monovalent G1P[8] vaccine since March 2006 [190]. This introduction was followed by a decrease in rotavirus-associated cases. The homotypic (G1 or P[8]) strains disappeared and a rise and spread of G2P[4] was seen.

When rotavirus vaccination is implemented in a NIP, it has to be fitted in the existing vaccination schedules. In the NIP of Australia, the combined diphteria, tetanus and pertussis (DTaP) vaccine is scheduled at 2, 4 and 6 months of age. In July 2007, rotavirus vaccine (RotaTeq) was introduced in the NIP with the same schedule as DTaP. Different from other vaccines, current recommendations for available rotavirus vaccines require that the first dose of vaccine should be administered before 15 weeks of age when background rates of intussusception are low and subsequent doses are administered with a minimal time interval of four weeks between doses. Introduction of the rotavirus vaccine has demonstrated to modestly increase timeliness of doses 1 and 2 of DTaP vaccination, and a definite increase of timely uptake of the 3rd dose of DTaP vaccine [191].

5.1.6.1 Cost-effectiveness

Postma et al. reviewed available cost-effectiveness models for rotavirus vaccination [192]. It was found that despite differences in the approaches and individual constituting elements including costs, QALYs, and deaths, cost-effectiveness results of the models were quite similar. Sensitivity analysis revealed cost-effectiveness of rotavirus vaccination is highly sensitive to vaccine prices, rotavirus-associated mortality and discount rates, in particular for QALYs. Bruijning et al. investigated cost-effectiveness of targeted rotavirus (RV) vaccination of high-risk infants and universal vaccination in the Netherlands (submitted). In this study, an age-structured stochastic multi-cohort model of the Dutch population was developed comparing universal RV vaccination and targeted vaccination of high-risk infants to no vaccination. The model included disease burden, mortality and healthcare costs of RV hospitalisation for children with and without prematurity, low birth weight and congenital pathology as

derived from the epidemiological study on rotavirus hospitalisations conducted in the Netherlands which is discussed earlier in this chapter. Targeted RV vaccination was highly cost-effective and potentially cost-saving from the healthcare perspective with ICERs below € 20,000/QALY in all scenarios tested with total (undiscounted) healthcare costs between -€ 0.1 and € 0.5 million/year. Universal vaccination was not considered cost-effective (mean ICER: € 60,200/QALY). However, if herd-immunity was enclosed and vaccine prices were € 60 at most, universal vaccination was likely to be cost-effective (mean ICER: € 21,309/QALY). (Data not yet published)

5.2 Varicella zoster virus (VZV) infection

E.A. van Lier, H.J. Boot†, J.M. Kemmeren, A.W.M. Suijkerbuijk, A.K. Lugnér, W. Luytjes, I. Stirbu-Wagner, *P. Jochemsen, H.E. de Melker*

5.2.1 Key points

- No striking changes occurred in the VZV epidemiology in the Netherlands in 2011.
- 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.
- The incidence of GP consultations due to varicella in the Integrated Primary Care Information (IPCI) database is slightly higher than according to routine surveillance data (CMR/LINH). However, with regard to patients requiring hospitalisation estimates from IPCI are comparable to routine surveillance data (LMR). These results confirm the somewhat lower disease burden due to varicella in the Netherlands compared to other countries.

5.2.2 Epidemiology

5.2.2.1 Disease

5.2.2.1.1 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 Continuous Morbidity Registration (CMR) Sentinel General Practice Network and the Netherlands Information Network of General Practice (LINH) (Table 13) [193-195]. Starting in 2008, the Sentinel GP Network has changed from registration on paper to electronic reporting, which may have resulted in underreporting of the weekly number of varicella patients [193]. Therefore, we used data for varicella surveillance based on ICPC codes in electronic medical records (EMRs) from LINH and sentinel general practices combined from 2008 onwards. For herpes zoster, the LINH registration has already been in use from 2002 onwards.

Table 13 Incidence of GP consultations per 100,000 due to varicella or herpes zoster in 2000-2011 (rounded off to tens).

Syndrome	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Varicella*	200	240	320	270	250	190	300	210	(160)	(110)	(180)	-
Varicella**	-	-	190	160	200	130	260	230	290	180	210	230
Herpes zoster*	330	320	-	-	-	-	-	-	-	-	-	-
Herpes zoster**	-	-	320	330	310	350	370	310	340	360	360	360

*Continuous Morbidity Registration (CMR) Sentinel General Practice Network [193, 195].
**Netherlands Information Network of General Practice (LINH) [194].

From literature it is known that periodic larger outbreaks of varicella occur with an inter-epidemic cycle of two to five years [196]. In contrast, the incidence of herpes zoster is stable over the years, which is consistent with the literature [197]. The incidence of GP consultations per 100,000 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 20) [193-195].

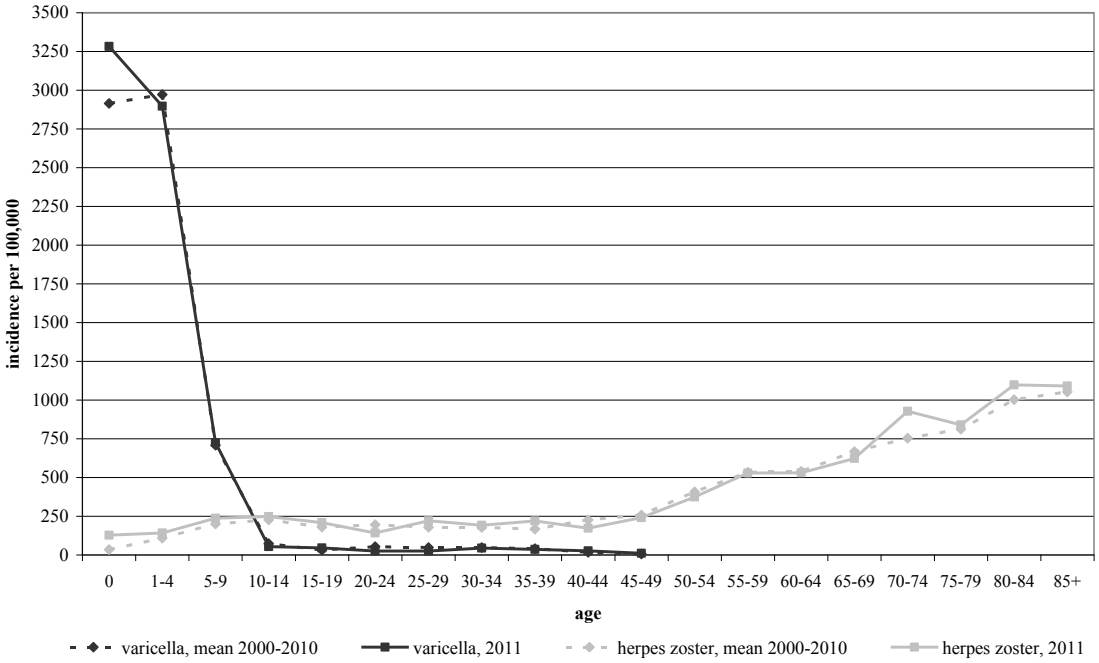


Figure 20 Incidence of GP-consultations per 100,000 for varicella and herpes zoster in 2011 versus mean incidence in 2000-2010 [193-195]. Note: varicella cases in persons older than 49 are only sporadically reported by GPs and are therefore not included.

5.2.2.1.2 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 National Medical Registration [198]; the incidence per 100,000 population is displayed in Table 14. 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 which 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

2000-2011. 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 21).

Table 14 Incidence per 100,000 of hospitalisations due to main and side diagnosis varicella or herpes zoster, 2000-2011 [198].

Syndrome	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Varicella – main	1.3	1.5	1.4	1.7	1.7	1.5	1.9	1.4	1.7	1.5	1.9	1.7
Varicella – main + side	2.0	2.3	2.2	2.5	2.6	2.2	2.8	2.1	2.4	2.2	2.7	
Herpes zoster - main	2.3	2.5	2.7	2.2	2.5	2.2	1.9	2.0	2.0	2.4	2.1	2.1
Herpes zoster – main + side	5.0	4.9	5.1	4.9	5.0	4.3	3.9	3.9	3.8	4.5	4.5	

Note: In 2006/2007 a number of hospitals stopped their registration, causing an underestimation of hospital admissions from 2006 onwards (see section 2.1.2.2).

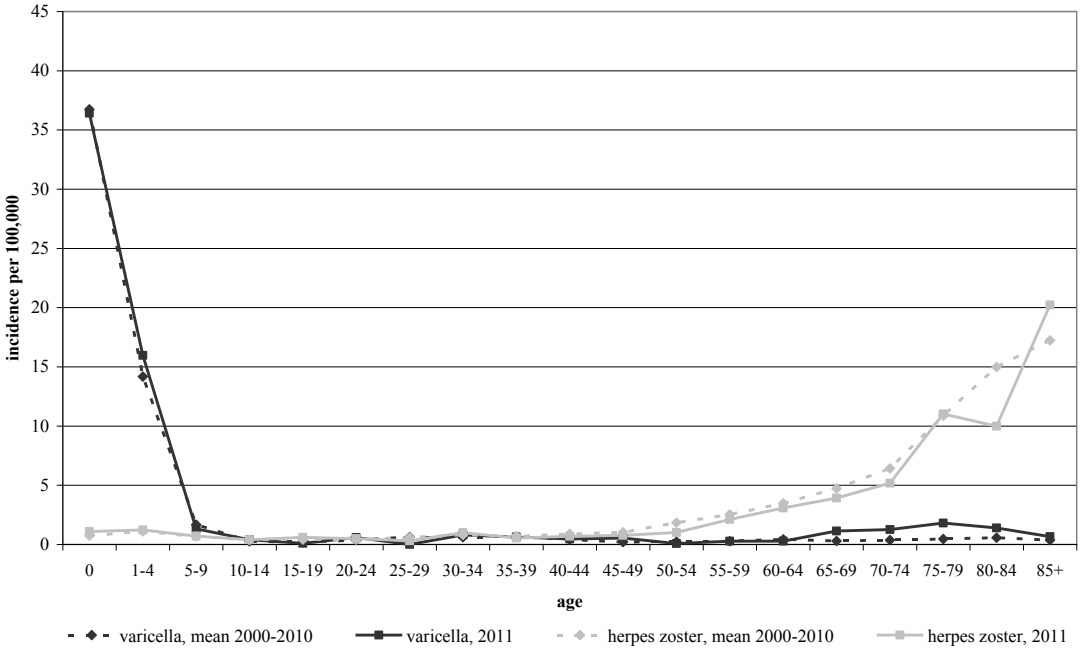


Figure 21 Incidence of hospitalised patients per 100,000 for main diagnosis varicella and herpes zoster in 2011 versus mean incidence in 2000-2010 [198].

If we define hospitalisation rate as the number of hospitalised patients divided by the number of GP consultations, we see the hospitalisation rate is high among the youngest age groups and rises with age for varicella in particular (Figure 22).

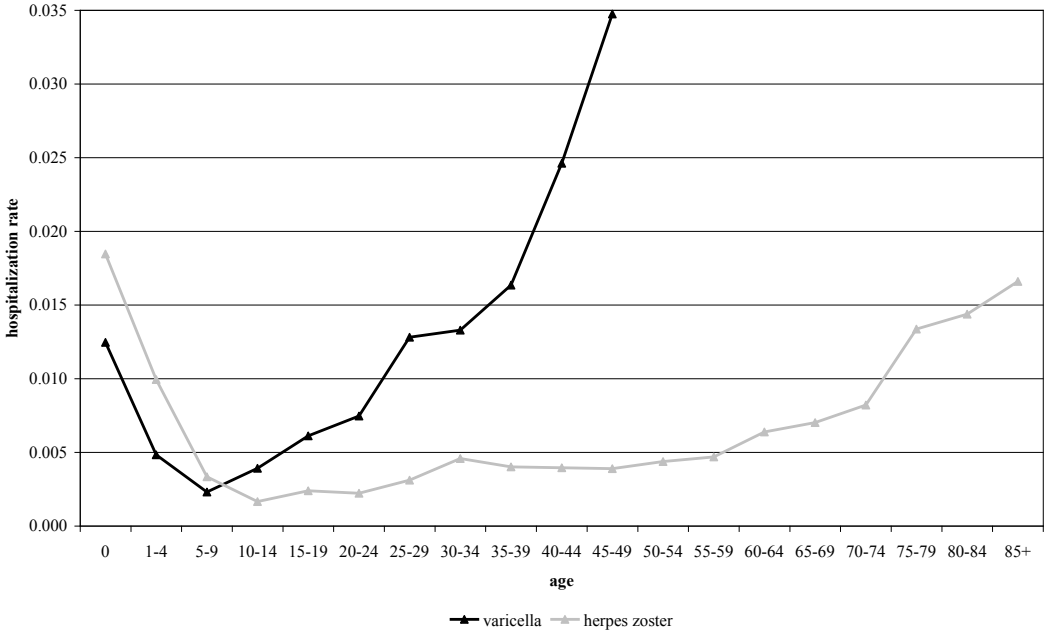


Figure 22 Mean hospitalisation rate 2000-2011 (number hospitalised patients [198]/ number of GP consultations) [193-195].
Note: varicella cases in persons older than 49 are only sporadically reported by GPs and are therefore not included.

5.2.2.1.3 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 15) [199]. In 2011, there was one reported death with main cause of death varicella and 20 deaths with main cause of death herpes zoster. It is known that national death certificate data greatly overestimates deaths in which herpes zoster is the underlying or contributing cause of death [200]. Mahamud et al. concluded most decedents for whom herpes zoster was determined not to be the underlying or contributing cause of death had a history of herpes zoster according to the medical record but did not have an active disease that resulted in or contributed to death. Errors in determining the underlying cause of death are more likely for decedents with several diseases (herpes zoster occurs primarily among elderly with multiple comorbid conditions), especially if detailed medical information is not available to the certifying physician. If we apply their rate (0.25 (range 0.10–0.38) per 1 million population before introduction of vaccination) of deaths in which herpes zoster was validated as the underlying cause of death on the Dutch population in 2011 we would expect 4.2 deaths (range 1.7–6.3) [200].

Table 15 Number of deaths with main cause of death varicella or herpes zoster, 2000-2011 [199].

Syndrome	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Varicella	1	3	4	6	4	1	3	5	0	1	2	1
Herpes zoster	14	13	26	14	15	15	24	21	14	20	25	20

5.2.2.2 Immune surveillance

The first cross-sectional population based serosurveillance study performed in 1995/1996 in the Netherlands (PIENTER 1) showed the Dutch population is infected with VZV at relatively young age: at least 95% of the six year olds had

antibody levels above the cut-off for VZV seropositivity [201]. The PIENTER 2 study, conducted in the Netherlands in 2006/2007, confirmed the young age of VZV infection in the Netherlands which was already found in PIENTER 1 (Figure 23) [202]. Among children younger than six years of age (children 0-6 months excluded), the following risk factors were significantly associated with VZV seropositivity in a multivariable logistic regression analysis: age, ethnicity and frequency of child day care center attendance.

Social contacts play an important role in the spread of VZV. Children with many contacts with 0-4 year olds are infected at an earlier age than children with lower number of contacts. Additionally, ethnicity and frequency of child day care centre attendance are factors which influence the age at infection [203].

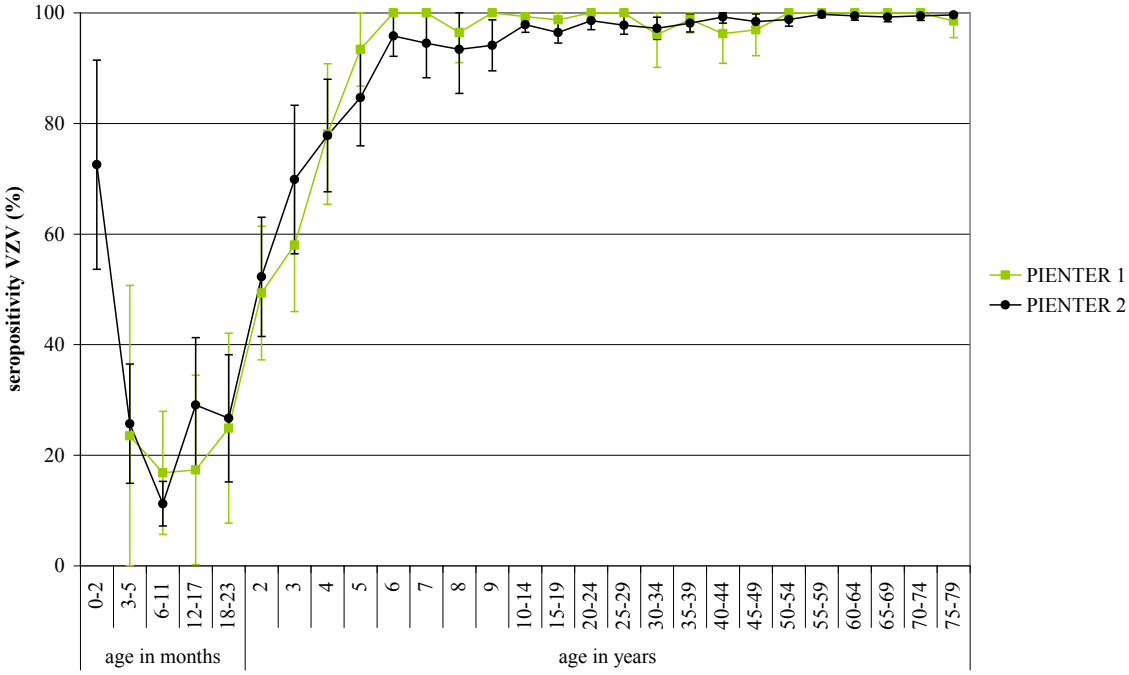


Figure 23 Age-specific seroprevalence for varicella zoster virus (VZV), with 95% confidence intervals – PIENTER 2 (2006/2007) versus PIENTER 1 (1995/1996) [201, 202].

5.2.3 *Pathogen*

VZV isolates can be divided in five defined clades and four provisional clades on the basis of phylogenetic analyses of whole-genome sequences [204]. Worldwide 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 [205]. Although recombination of strains belonging to different clades has been reported (including the OKA-vaccine clade 2 strain) [204, 205], no impact of recombination on vaccine effectiveness is currently evident. There are, however, indications that in Europe the clade distribution is shifting, due to importation of viral strains from other areas, such as Africa, and that these strains spread more effectively in the population than strains belonging to European VZV clades [206]. This is of interest since not all clades might lead to reactivation in the same order of magnitude. A difference in frequency of reactivation might also have therapeutical consequences. Furthermore, there are indications that some strains give rise to infection at younger age than others [205, 206]. Introduction of universal varicella and/or zoster 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

MMRV vaccination in 4-6 year old children is not associated with an increased risk of febrile convulsion [46]. The increased risk of febrile convulsion in younger children has a negative impact on the recommendation of MMRV by physicians in the US [207]. The CDC recommends MMR vaccine and varicella vaccine should be administered for the first dose in this age group.
Several studies showed concomitant administration of varicella vaccine with other childhood vaccines like MMR [46], PCV-7 [90], HibMenCY-TT [105] and MMR + hepatitis A vaccines [208] is generally well tolerated. The SmPC of Proquad is updated in 2012 with the findings that Proquad can be given concomitantly with either Prevenar and/or Hepatitis A vaccine or with monovalent or combination vaccines comprised of diphtheria, tetanus, acellular pertussis, *Haemophilus influenza* type b, inactivated poliomyelitis or hepatitis B antigens.
Varicella vaccine was also well tolerated in the SLE (systemic lupus erythematosus) group who had pre-existing immunity to varicella [209] and in patients at hematopoietic cell transplantation [210]. Fridman et al. [211] found a second dose of Varicella Biken was well tolerated and showed no significant safety issues in a population of previously vaccinated children.
In ProQuad – a vaccine containing antigens from MMRVAXPRO and VARIVAX – recombinant human albumin (rHA) was selected as a replacement for human serum albumin (HSA) to eliminate blood-derived products of human origin from the manufacturing process of the MMRV vaccine. Two studies demonstrated good safety profiles of MMRV manufactured with rHA [212, 213].

5.2.4.2 Herpes zoster vaccination

For zoster vaccination, Zostavax is the only registered vaccine. The EMA has granted a renewal of the marketing authorisation with the requirement of one additional renewal due to the limited use of Zostavax in the EU. The SPC has been updated: nausia is added as adverse reaction as post marketing reports suggest a temporal relation between vaccination and nausea. The reactogenicity is slightly higher in subjects of 50 to 59 years old than in subjects ≥ 60 years of age [214].
Several studies evaluated the safety of herpes zoster vaccination in adults. In subjects aged 50-59 years [215] as well as in adults ≥ 60 years [216, 217] zoster vaccine was generally safe and well-tolerated. Tseng et al. [218] support these findings but also found a small increased risk of allergic reactions 1-7 days after vaccination. Zhang et al. [219] examined the association between herpes zoster vaccination and herpes zoster incidence in patients with selected immune-mediated diseases. However, no such association was found.
A phase I/II parallel-group study compared the safety of an adjuvanted recombinant varicella zoster virus subunit vaccine with a live attenuated Oka strain VZV vaccine in young adults [220]. No severe events were reported. Fatigue, myalgia, headache and injection site pain were the most common reported reactions for the adjuvanted subunit vaccine and occurred more frequently than with OKA. However, the adjuvanted subunit vaccine was overall well tolerated.

5.2.5 Current/ongoing research

Insight into the disease burden of varicella in the Netherlands is essential in the decision making process whether or not to introduce routine childhood varicella vaccination in the Netherlands. Therefore it is important to know whether the number of GP consultations and hospitalisations due to varicella based on routine surveillance data give the full picture or if there is considerable underreporting.

5.2.5.1 Incidence

An alternative data source for the number of GP consultations is the Integrated Primary Care Information (IPCI) database from Erasmus MC, Universal Medical Center. This is a longitudinal GP research database for which data collection started in 1996. The database presently contains over one million patients records from more than 400 GPs in the Netherlands [221-223]. Within this IPCI database we identified varicella patients in the period 2006-2008 according to the following procedure: all patients with the International Classification of Primary Care (ICPC) code A72 (chickenpox) and all patients with the text 'waterpokken', varicella, VZV or chickenpox in the free text fields of the medical journal were considered potential varicella patients. Subsequently, all these potential varicella patients were manually validated and the diagnosis was divided into the following categories: 1=no varicella, 2=varicella, 3=probable varicella, 4=herpes zoster, 5=person has been in contact with someone with (probable) varicella but had no symptoms himself. Subsequently we calculated a low (only code 2=varicella) and high (sum of code 2=varicella and code 3=probable varicella) incidence estimate for GP consultations due to varicella, standardised to the Dutch population by age and sex. Preliminary results showed that the low IPCI estimate is somewhat higher for 2006 and 2007 and somewhat lower for 2008 than the routine CMR Sentinel GP Network [193] and LINH [194] estimates (Table 16). If probable varicella cases were included as well (high IPCI estimate), the incidence estimate is of course higher but not as high as the incidence estimate from Zorggroep Almere (ZGA) [224] (Table 16). This latter study of Pierik et al. also identified probable varicella patients based on the ICPC-code A72 and free text in the medical journal; their results were also standardised to the Dutch population. According to this study the annual overall incidence of GP consultations in 2004-2008 was 515 per 100,000 but when only ICPC coded diagnoses were included, the annual overall incidence was 377 per 100,000. A possible explanation for the difference between the high IPCI estimate and ZGA could be differences in population characteristics (ethnicity, socio-economic factors). From the PIENTER 2 study [202] it is known that the seroprevalence is lower among people with a non-Dutch ethnicity; in Almere the percentages immigrants (38%) and in particular non-western immigrants (28%) are considerably higher than in the total Dutch population (21% and 12% respectively) [225]. In Belgium the incidence of GP consultations due to varicella was recently estimated to be 346 per 100,000 [226]. Wolleswinkel-van den Bosch et al. found only 38% of the Dutch parents within their internet survey consulted a physician when their child was ill with varicella [227].

Table 16 Incidence of GP consultations per 100,000 due to varicella by calendar year in the Integrated Primary Care Information (IPCI) database (preliminary results), the CMR Sentinel GP Network [193], the Netherlands Information Network of General Practice (LINH) [194] and Zorggroep Almere (ZGA) [224].

Year	IPCI low estimate	IPCI high estimate	CMR	LINH	ZGA
2006	351	411	300	260	492
2007	268	320	210	230	583
2008	266	355		290	566

5.2.5.2 Hospitalisation

Medical record research among patients hospitalised with main or side diagnosis varicella in 2003-2006 according to the National Medical Register, showed varicella complications occurred in the majority (76%) of hospitalised patients [228]. Bacterial super infections of skin lesions (28%), (imminent) dehydration (19%), febrile convulsions (7%), pneumonia (7%) and gastroenteritis (7%) were most frequently reported. A considerable part of all complications (70%) was rather moderate and could be treated effectively, although in 37% of the hospitalised cases, at least one relatively severe complication occurred. The median duration of admission for all patients in this study was 3.6 days. In a considerable part of patients (26%), varicella was incorrectly registered in the LMR as side diagnosis instead of main diagnosis. Moreover, almost half (45%) of the varicella complications as retrieved from the medical record was not registered as such in the LMR. A considerable part of the 225 patients with complications were incorrectly registered in the LMR as 'varicella without complication (ICD-9 code 052.9)' (66%) or as 'varicella with unspecified complication (ICD-9 code 052.8)' (7%); sometimes despite the fact that additional codes were registered in the LMR which were very likely complications caused by varicella.
Within the IPCI data we also identified hospitalised varicella patients (Table 17). Preliminary results showed the estimated incidence according to IPCI are in the same order of magnitude as the LMR estimates [198]. In Belgium, the incidence of hospitalisations due to varicella was recently estimated to be higher with 5.3 per 100,000 [226].
Pierik et al. did not provide information on hospital admission separately, but calculated the incidence (8.6 per 100,000 in the period 2004-2008) of consultations for varicella in hospital care in general, including consultation of a specialist [224]. Preliminary results from the IPCI data show the incidence of patients having contact with hospital care (either hospital admission or a consult with the emergency department/specialist) is with 7.1 per 100,000 in the same order of magnitude.
Thus, the IPCI data confirm the earlier findings of a lower disease burden due to varicella in the Netherlands compared to other countries.

Table 17 Incidence of hospital admissions per 100,000 due to varicella by calendar year in the Integrated Primary Care Information (IPCI) database (preliminary results) and the National Medical Register (LMR) [198].

Year	IPCI	LMR main diagnosis	LMR main + side diagnosis
2006	2.7	1.9	2.8
2007	1.9	1.4	2.1
2008	1.8	1.7	2.4

Note: In 2006/2007 a number of hospitals stopped their registration, causing an underestimation of hospital admissions from 2006 onwards (see section 2.1.2.2).

5.2.5.3 Other

In 2013, additional results (number and type of visits per patient, prescriptions, complications and referrals to a specialist) from the IPCI study will become available. Seroprevalence data from the PIENTER study and incidence data from different data sources will be used in a 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, are under evaluation to achieve the most effective vaccination schedule for the NIP. This information will be used in cost-effectiveness analysis. Research on the willingness of parents to vaccinate their child against potential new vaccine candidates for the NIP, including varicella, has also been prepared.

5.2.6 International developments

Recently, three European economic evaluations have been published favouring herpes zoster vaccination for the elderly and a combined varicella and zoster vaccination strategy. However, a review of varicella vaccination in the United States ascertained that universal vaccination is not economically attractive.
Szucs et al. evaluated the clinical and economic impact of a herpes zoster vaccination program for adults aged 70–79 years in Switzerland [229]. A vaccination strategy compared to no-vaccination resulted in lifetime incremental cost-effectiveness ratios of US $ 23,646 per QALY gained and US $ 6,134 per herpes zoster case avoided, and US $ 14,340 per post-herpetic neuralgic pain case avoided. In this article, a Markov model was used, simulating the natural history of herpes zoster and post-herpetic neuralgia and the lifetime effects of vaccination, adapted to the Swiss context. The model predicts clinical and economic benefits of vaccination in the form of fewer herpes zoster and post-herpetic neuralgic pain cases and reductions in healthcare resource use. Since ICER's were within the commonly accepted thresholds in Switzerland, a herpes zoster vaccination programme would be considered a cost-effective strategy in the Swiss setting.
Bilcke et al. also assessed the cost-effectiveness of vaccinating the elderly against herpes zoster in Belgium [230]. They found that under assumptions least in favour of vaccination, vaccination would not be cost-effective (i.e. incremental cost per QALY gained > € 48,000 for all ages considered) at the expected vaccine price of € 90 per dose. At the same price, under the most favourable assumptions, vaccination would be cost-effective (ICER < € 5500 per QALY gained for all ages considered). If the vaccine price per dose drops to € 45, herpes zoster vaccination of adults aged 60–64 years is also likely to be cost-effective in Belgium, even under the least favourable assumptions.

Bilcke et al. acknowledged that an accurate estimation of herpes zoster vaccine efficacy by time since vaccination and age at vaccination is hampered by lack of insight in the underlying biological processes and by limited data [231]. A recent publication of Schmader et al. showed there is evidence for persistence of herpes zoster vaccine effectiveness through year 5 post vaccination; beyond this point the efficacy is unknown [232].

Although there have been a large number of economic analyses of varicella vaccination, only a small number of previous cost-utility analyses have taken into account the possible impact of varicella vaccination on the incidence of herpes zoster. Van Hoek et al. assessed the cost-effectiveness of combined varicella and zoster vaccination options and compared this to alternative programmes in the UK [233]. In this article, a transmission dynamic model was used in which social mixing patterns and UK data on varicella and zoster incidence were included. The results of the incremental cost-effectiveness analysis suggested a combined policy is cost-effective. However, the cost-effectiveness of the childhood two-dose policy is influenced by projected benefits that arise after many decades (80–100 years or more), following the start of vaccination. If the programme is evaluated over a shorter time horizon, it would probably not be cost-effective and may result in increased disease burden, due to a rise in the incidence of herpes zoster. In conclusion, the potential negative benefits in the first 30–50 years after introduction of a childhood varicella vaccine can only be partly mitigated by the introduction of a herpes zoster vaccine.
Goldman & King reviewed the effects of the universal varicella vaccination which was introduced in the United States in 1995 [234]. Initially, varicella case reports decreased by 72%, from 2834 in 1995 to 836 in 2000 at which time approximately 50% of children under 10 years of age had been vaccinated. Since varicella vaccination has failed to provide long-term protection from varicella zoster virus disease, an additional booster vaccine for children and a herpes zoster vaccine to boost protection in adults was necessary. According to Goldman & King, the proponents for universal varicella vaccination have failed to consider an increase of herpes zoster among adults as well as the adverse effects of both the varicella and herpes zoster vaccines, which have more than offset the limited benefits associated with reductions in varicella disease. For that reason they concluded that universal varicella vaccination has not proven to be cost-effective in the United States.

5.3 Hepatitis A

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

5.3.1 Key points

- In 2011, the number of hepatitis A infections (125 cases) was the lowest since this became notifiable in 1999.
- Almost half of the Dutch cases (45%) were reported to be travel-related.

5.3.2 Epidemiology

In 2011, 125 cases of hepatitis A were reported in the Netherlands corresponding to 0.8 cases per 100,000 inhabitants. This was the lowest number since hepatitis A became notifiable in 1999 (Figure 24 / Appendix 2). One of five reported patients was hospitalised, similar to 2010 and higher than in the years 2003-2009 (8-18%). The mean age of patients hospitalised with a hepatitis A infection was 37 years (range 7-75 years, 20% aged <19 years) compared to

25 years of age (range 1-81 years, 46% aged <19 years) in non-hospitalised patients. No mortality due to hepatitis A was reported. Since 1999, nine fatal hepatitis A infections have been registered, only among adults.

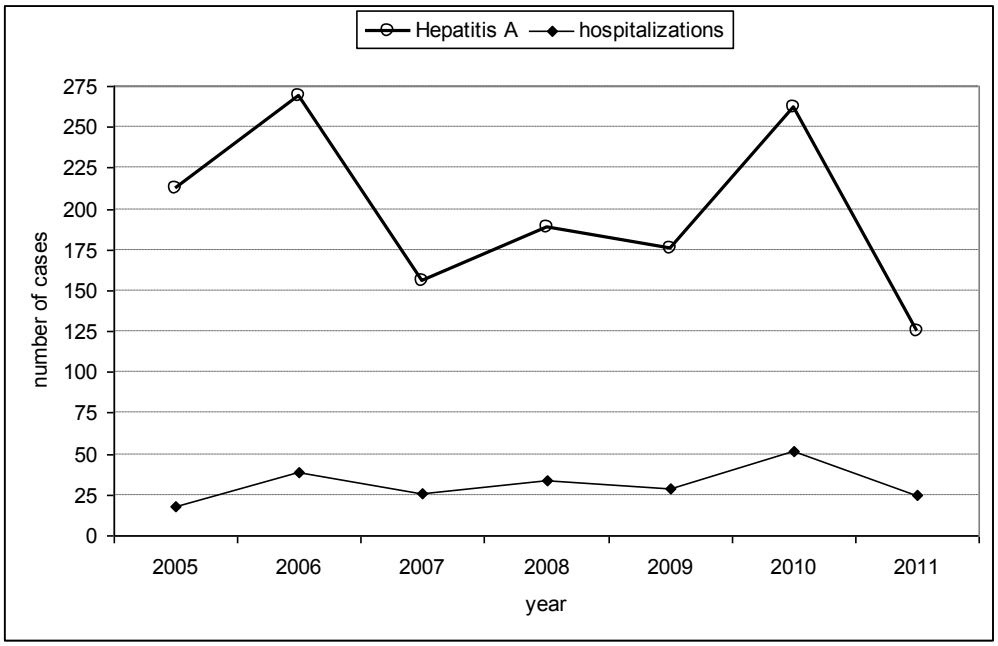


Figure 24 Number of reported and hospitalised cases of hepatitis A, 2005-2011.

Almost half of the cases in 2011 (45%) were reported to be travel-related, which is comparable to the years 2005-2009 (43-54%). Only in 2010, 31% of the cases reported was travel-related. Morocco was mentioned most (26 cases; 20.8%), followed by Egypt and India (both 4 cases; 3.2% each) and Turkey (3 cases; 2.4%). For about one-third of the cases the most likely source of infection was contact with another infected person. Twenty-two cases reported food as the most likely source and a cluster investigation led to a further six cases probably infected via contaminated ready-to-eat salad [235], resulting in 28/125 (22%) probable foodborne infections, of whom 21 cases implied food consumed abroad.

5.3.3 Pathogen

IgM-positive samples can be send to the LIS of the RIVM for typing as part of the molecular surveillance of hepatitis A cases. Also, faecal samples can be sent for diagnostics if a serum sample is not preferred to be taken. This is often preferred for young children who are not ill but are possibly related to a cluster. In 2011, a total of 295 serum and faecal samples were tested, of which 114 samples were positive and 96 (84%) also could be typed, resulting in 46 unique sequences of which 14 clusters of 2 to 13 cases.

5.3.4 Adverse events

In a systematic review to determine the efficacy and safety for inactivated and live attenuated hepatitis A vaccines, Irving [236] showed the risk of both non-serious local and systemic adverse events was comparable to placebo for the inactivated hepatitis A vaccines. There were insufficient data to draw conclusions on adverse events for the live attenuated hepatitis A vaccines.
One study was conducted to assess the safety of inactivated hepatitis A vaccines concomitantly given with other childhood vaccines. It demonstrated the

coadministration of hepatitis A vaccine with MMR and varicella vaccines was well tolerated [237]. Two studies in China evaluated the interchangeability between Chinese domestic inactivated hepatitis A vaccine (Healive) and imported inactivated hepatitis A vaccines (Havrix) [238, 239]. No differences of reported adverse reactions across the groups were found.

5.3.5 Current/ongoing research

Initially, the typing of IgM-positive samples by the LIS 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 notifications, where possible, to combine the available information about microbiology and epidemiology. In case of a cluster of cases where dates of illness onset lie close together, mostly an outbreak investigation is started to find out the cause.

5.3.5.1 Cost-effectiveness

Suijkerbuijk et al. [240] assessed the potential benefits and drawbacks of introducing hepatitis A vaccine in the NIP in the Netherlands. Since future cohorts of non-vaccinated elderly will lack protection against disease, this could be an argument in favour of taking preventive measures such as including hepatitis A vaccine into the NIP, or offering hepatitis A vaccine to the elderly only [241]. Initiating a vaccination program would most likely not be cost-effective yet. The annual costs of mass-vaccination are large: about € 10 million for infants and € 13 million for older people (only in the first year € 210 million), based on current retail prices. The annual effects of mass-vaccination are small: the cost-of-illness in recent years attributed to hepatitis A infection is estimated to be € 650,000 per year, and the disease burden is on average 17 DALYs. Given the continuing decline in incidence, targeted preventive measures such as vaccinating travellers and other high-risk groups and timely vaccination of close contacts of hepatitis A patients are adequate. However, because susceptibility to hepatitis A is increasing in the group with the highest risk of developing severe complications upon infections, careful monitoring of the epidemiology of hepatitis A remains important.

5.3.6 International developments

Ott et al. [242] reviewed the long-term protective effect of live attenuated and inactivated hepatitis A vaccines. The maximum observation time and reported level of seroprotective anti-HAV antibodies for live attenuated hepatitis A was fifteen years, with higher numbers of doses leading to higher seropositivity. The maximum for inactivated hepatitis A was fourteen years without a significant effect of dosage and schedule of vaccination. Van Herck et al. [243] reported a long-term persistence of hepatitis A vaccine-induced antibodies based upon seventeen years of follow-up after vaccination of healthy adults with a two-dose inactivated hepatitis A vaccine (Havrix). At year 17, 97-100% of the vaccinated individuals was still seropositive for anti-HAV antibodies. Hendrickx et al. [244] state in their review on hepatitis A, B and E vaccines that the high immunogenicity of the hepatitis A vaccines in general as well as the vaccine intervention data in outbreaks suggest a single dose may be sufficient to prime the immune response and interrupt the transmission in the community. Eighty-nine to 100% of children immunised with a two-dose hepatitis A vaccine before the age of two years retained seroprotective anti-HAV levels for at least ten years, regardless of the presence of maternal anti-HAV [245].

5.4 Meningococcal serogroup B disease

T.M. van 't Klooster, M.J. Knol, P. Kaaijk, N.Y. Rots J.M. Kemmeren, H.E. de Melker, A. van der Ende, G.A.M. Berbers

5.4.1 Key points

- The incidence of meningococcal B disease had decreased further in 2011.
- A meningococcal B vaccine is currently under regulatory consideration (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 25 and Table 18. In 2011, the number of cases had decreased to 69. The reason for this decreased incidence remains enigmatic. Possibly, natural fluctuation may explain this decreasing trend. In 2012 up to July, the number of MenB cases amounted to 40. More than 50% of the cases concerned children aged younger than five years.

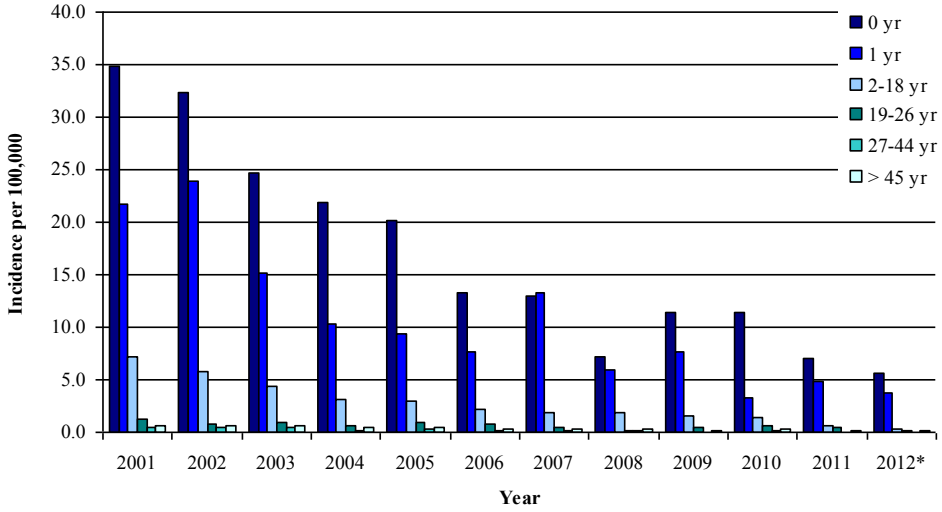


*Figure 25 Age-specific incidence of MenB disease, 2001-2012. *Until July.*

Table 18 Absolute number of patients with MenB disease per age-category from 2001-2012.

Age (Yrs)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012*
0	69	66	50	44	39	25	24	13	21	21	13	10
1	45	50	31	21	19	15	25	11	14	6	9	7
2-18	236	195	147	106	103	74	66	65	54	48	22	10
19-26	19	12	14	10	15	12	8	3	8	11	8	2
27-44	20	20	21	10	11	9	7	5	3	5	2	3
44-99	38	42	38	31	28	20	21	26	13	22	15	8
Total	**427**	**385**	**301**	**222**	**215**	**155**	**151**	**123**	**113**	**113**	**69**	**40**

*Until July.

5.4.3 *Pathogen*

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

5.4.4 *Adverse events*

Two phase I and one phase II trials assessed the safety of an experimental MenB vaccine. This bivalent recombinant lipoprotein 2086 vaccine was generally well-tolerated [246]. A phase 2b/3 placebo-controlled study assessed the tolerability of a four-component MenB vaccine[247]. It showed local and systemic reaction rates were similar after each 4CMenB injection and did not increase with subsequent doses, but remained higher than placebo. No vaccine-related serious adverse events (SAE) were reported and no significant safety signals were identified.

5.4.5 *Current/ongoing research*

An improved nonavalent PorA native outer membrane vesicle vaccine has been developed by NVI/RIVM with intrinsic adjuvating activity due to presence of less-toxic (lpxL1-)LPS [248]. The safety and immunogenicity of this next-generation NonaMen vaccine has been evaluated following repeated vaccination in rabbits and mice [249]. With respect to safety, no relevant toxicological findings have been observed. Based on the confined temperature rise in rabbits after vaccination [250] and the limited in vitro induction of the pro-inflammatory cytokine, interleukin-6 (IL-6), by the human monocytic cell line (MM6) after exposure with the vaccine, NonaMen is expected to be non- or low pyrogenic [247]. In both rabbits and mice, NonaMen induced high serum bactericidal activity (SBA) against all tested MenB strains regardless of whether or not aluminium phosphate adjuvant was used [249]. These data suggest next-generation NonaMen is a safe vaccine with the potential to develop a broadly protective immune response and encourage the start of the first clinical studies.

A clinical study to determine the carrier state of the various meningococcal serogroups among different age groups is planned to be initiated in 2013. This provides the opportunity to investigate the possible effects on carriage serogroup replacement following vaccination with a new MenB vaccine when this might be implemented in the future.

5.4.6 *International developments*

Several MenB vaccines are currently under development, which aim to offer broad protection. These include a range of formulations differing in composition and complexity: 4CMenB (Bexsero, Novartis) [251] and rLP2086 (Pfizer) [252], containing multiple recombinant protein components respectively with and without an outer membrane vesicle (OMV) component; OMV-based vaccines such as NonaMen [247] (RIVM) and a trivalent native OMV vaccine are currently under development at the Walter Reed Army Institute of Research (WRAIR) [253]. Several of these vaccines are at the clinical stage of development and 4CMenB has given a positive opinion from the EMA. With the exception of the rLP2086 concept which aims to protect the adolescent age group, the other vaccines have been developed to protect infants against MenB invasive meningococcal disease (IMD).

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 the

vaccine that was used to control the outbreak in New Zealand (PorA P1.7-2,4, MeNZB). The putative wild type MenB strain coverage of this vaccine varies from 90% in the US to 65% in Spain.
The immunogenicity of the vaccine has been demonstrated in various large Phase III clinical trials [250]. Novartis reports that at present, the vaccine has been investigated in studies involving more than 8,000 infants, adolescents and adults. It is striking the vaccine is still not licensed, while in December 2010 a marketing authorisation application was already submitted in Europe and in other countries, including a proposed infant vaccination schedule. Probably, a number of regulatory issues are the cause of this delay.
The comparatively low incidence of MenB disease in most countries means that licensure based on direct evidence of protection is not feasible. Instead, SBA, an accepted correlate of protection against IMD, has been used as a surrogate endpoint for Men B vaccine efficacy. The challenge has been how to assess the prospective breadth of coverage of new formulations against the diverse MenB strains. Given the small volume of serum obtained from infants in clinical trials and the complexity of the assay, there is a limit to the number of strains that can be used to measure SBA. Consequently, vaccine manufacturers have made predictions of the potential coverage of their vaccines, using antibody assays to determine the level and specificity of the vaccine antigens expressed on the bacterial surface of relevant strains circulating in different geographical regions.
In October 2011, the WHO and Health Canada jointly organised a consultation on regulatory considerations to seek consensus on key regulatory issues regarding the evaluation of the immunogenicity of candidate MenB vaccines and to review safety issues with special focus on the induction of fever. In this meeting was concluded that a set of principles for the SBA should be developed, including information on the selection of strains, complement validation, serum panels etc. A standard panel of strains may help in assessing the performance of the assay in different laboratories. There was a consensus that instead of pyrogenicity testing in rabbits, the implementation of in vitro alternatives was more appropriate. This seems to be a step in the right direction for licensing a new MenB vaccine.

5.5 Meningococcal non-serogroup B and C types

T.M. van 't Klooster, M.J. Knol, P. Kaaijk, N.Y. Rots, .J.M. Kemmeren, H.E. de Melker, A. van der Ende, G.A.M. Berbers

5.5.1 Key points

- In 2011, 18 of the 89 meningococcal cases were non-serogroup B and C.
- The incidence of meningococcal serotype Y disease had increased further in 2011 in Europe and contributes up to 33% of the incidence in the USA.

5.5.2 Epidemiology

Since 2001, the number of patients with meningococcal serotype W disease has decreased to only one case in 2011, as can be seen in Figure 26 and Table 19. The number of meningococcal serotype Y cases has increased from 7 cases in 2009, to 11 cases in 2010 and 15 cases in 2011 (Figure 26 and Table 20). Until June 2012, 7 cases of meningococcal serotype Y were reported, of which one 51-year-old person deceased.
No MenA cases were reported in 2011 and 2012 up to July.

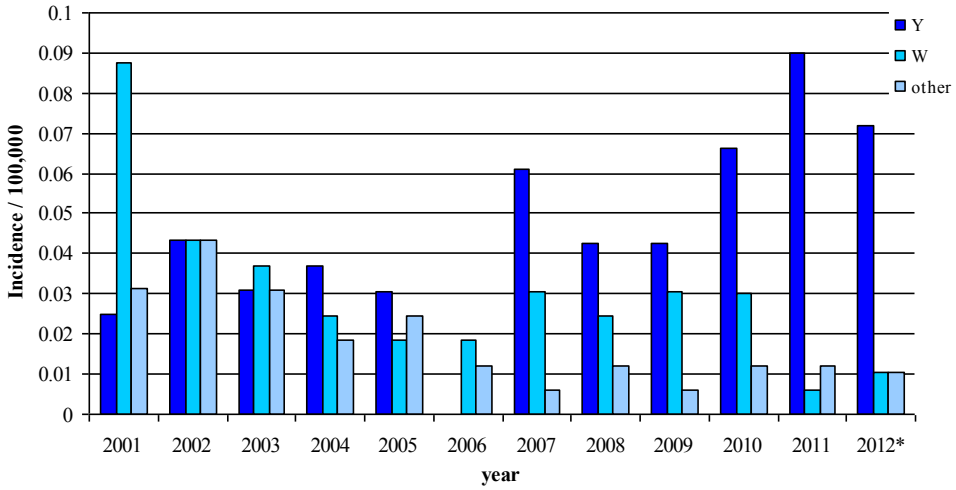


*Figure 26 Incidence of Meningococcal non-B and non-C types, 2001-2012. *Until July.*

Table 19 Absolute number of patients with MenW disease per age-category, 2001-2012.

Age (Yrs)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012*
0	3	1	0	0	1	0	1	0	0	0	0	0
1	0	0	3	0	0	1	1	1	1	1	0	0
2-18	3	2	1	0	1	1	1	0	1	2	1	0
19-26	1	0	0	0	0	0	0	1	0	0	0	1
27-44	3	1	0	0	0	1	1	0	1	0	0	0
45-99	4	3	2	4	1	0	1	2	2	2	0	0
Total	**14**	**7**	**6**	**4**	**3**	**3**	**5**	**4**	**5**	**5**	**1**	**1**

**Until July.*

Table 20 Absolute number of patients with MenY disease per age-category, 2001-2012.

Age (Yrs)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012*
0	0	0	1	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0	1	0	0
2-18	0	1	1	3	0	0	1	0	1	1	5	2
19-26	1	2	0	0	0	0	2	0	1	2	2	0
27-44	0	0	1	0	0	0	0	1	0	2	2	1
45-99	3	4	2	3	5	4	7	6	5	5	6	4
Total	**4**	**7**	**5**	**6**	**5**	**4**	**10**	**7**	**7**	**11**	**15**	**7**

**Until July.*

5.5.3 *Pathogen*

Neisseria meningitidis is differentiated into 12 distinct serogroups of which A, B, C, W, X and Y are medically most important.

5.5.4 Adverse events

See section 4.9.5.

5.5.5 Current/ongoing research

A clinical study to determine the carrier state of the various meningococcal serogroups among different age groups is planned to be initiated in 2013.

5.5.6 International developments

Before 1991, MenY caused 2% of all invasive meningococcal disease (IMD) cases in the US. Between 1997-2008 MenY accounted for approximately 25% of IMD cases in the US, which has now increased to a third of cases [247]. Recent epidemiological surveillance indicates MenY IMD is also emerging in some parts of Europe, especially in Scandinavia, Switzerland France and the UK [254]. The reasons for a dramatic shift in meningococcal serogroup distribution in some European countries are unknown. The increase of MenY IMD does not coincide with MenC conjugate vaccine uptake, making serogroup replacement an unlikely explanation [254].

Several meningoccal serogroup combination vaccines have been licensed in the US and European markets. The following combination vaccines containing the serogroup Y have been licensed for the European markets, including the Dutch market:

- Menveo (Novartis), a polysaccharide vaccine used to protect adults and children from the age of two years against IMD caused by MenA, C, W, Y.
- Nimenrix (GlaxoSmithKline) used to protect adults, adolescents and children from the age of 12 months also against IMD caused by the four serogroups (ACWY). Nimenrix offers the benefits of a conjugated vaccine over conventional polysaccharide vaccine, including a strong immune response in younger children below the age of 2 years.

In addition, Menitorix (GSK), a combination Hib-MenC conjugate vaccine, is licensed in various countries, although not in the Netherlands. This year, a combination of Hib-MenCY (MenHibrix; GSK) has also been approved by the FDA for marketing in the US.

6 Other possible future NIP candidates

N.Y. Rots, A.W.M. Suijkerbuijk, M.C. van Blankers, W. Luytjes

The aim of this chapter is to update information with regard to vaccines for infectious diseases which have reached the clinical testing phase and are relevant for the Netherlands. New combination vaccines in development are not included in this chapter.

In 2012, a new Jordan report on the accelerated development of vaccines became available [255]. In this report, a status of vaccine research and development is included.

6.1 Respiratory Syncytial Virus (RSV)

Respiratory Syncytial Virus (RSV) is a very common virus that leads to mild, common cold-like symptoms in adults and older healthy children. It can be more serious in young babies, especially to those in certain high-risk groups. It 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 six months of age. Premature infants and infants with congenital heart disease (CHD) or bronchopulmonary dysplasia (BPD) are particularly at risk of severe disease after RSV infection. Later in life, RSV causes primarily, sometimes severe, upper respiratory tract disease. However, immunocompromised individuals, persons with congenital heart disease and the elderly are at high-risk to develop lower respiratory tract disease. An effective vaccine might reduce the high burden of disease caused by RSV, but is not yet available.

In school-aged children wheeze is no longer associated with a history of RSV-hospitalisation. Meijboom et al. estimated 28,738 GP visits and 1,623 hospitalisations for children under one year of age due to RSV [256]. In the elderly, little data on morbidity is available. Based on a UK study [257] was estimated that in the Dutch population of 65 years and older, assuming that ~19% of this population are high-risk persons and the rest of the elderly are healthy, the annual incidence per 100,000 persons of RSV infections is 12,146, leading to 2488 GP visits and 541 hospitalisations (Meijboom, 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. In the US, where data exist primarily for the institutionalised elderly, this number has been reported to be 10 times higher.
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 in 2014, in a programme that is expected to take four years.

Meijboom et al. assessed the cost-effectiveness of a potential universal RSV vaccination in the Netherlands [256]. In this study, a decision analysis model was developed in which a Dutch birth cohort was followed for twelve months. A number of potential vaccination strategies was reviewed, such as vaccination at specific ages, a two- or three-dosing scheme and seasonal vaccination versus year-round vaccination. The total annual cost to society of RSV in the non-vaccination scenario is € 7.7 million and the annual disease burden is estimated at 597 QALYs. In case all infants would be offered a potentially safe and effective 3-dose RSV vaccination scheme at the age of 0, 1 and 3 months (at a vaccine price of € 37.50 per dose), the annual net costs will increase to € 21.2 million, but 544 hospitalisations and 1.5 deaths would be averted. The incremental cost-effectiveness ratio was estimated at € 34,142 per QALY gained. The outcomes of this study show vaccination of infants against RSV might be cost-effective. However, due to the absence of clinical trial data, a number of crucial assumptions had to be made related to the characteristics of the potential RSV vaccine, influencing the cost-effectiveness of universal vaccination.

6.2 Tuberculosis

Tuberculosis (TB) 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 higher risk. The vast majority of TB deaths – approximately two million people each year - occur in the developing world.
In 2011, in the Netherlands, the total number of TB patients dropped to 1007, which is 58 patients (5%) less than reported to the Nederlandse Tuberculose Register (NTR) in 2010 and 13% less than in 2009. The TB incidence in the Netherlands was 6.4 patients per 100,000 persons in 2011, in 2010 and 2009 the incidence was slightly higher, 6.5 and 7.0 per 100,000 persons respectively [258]. The majority (78%) concerns immigrants, 70% first generation and 8% second generation immigrants. More than half of the TB patients live in the provinces Zuid-Holland, Noord-Holland and Flevoland. Fiftyseven percent of the TB patients have been diagnosed with lung tuberculosis, for 2010 this was 56%. A growing concern is the steady increase in the number of TB cases which is resistant to most of the used medication.

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 to become 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 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, of which 95% in the developing world. Today AIDS is the leading cause of death in Africa and the fourth one worldwide.
In December 2011, a total of 19,231 HIV/AIDS patients were registered in the national database of the HIV treatment centers (SHM) in the Netherlands, including 811 newly HIV diagnosed patients, of which 797 were adults and 14 younger than 20 years. The number of newly diagnosed patients in 2011 can slightly increase in the upcoming years due to reporting delay. The majority, 79%, of the patients were male [259]. For 2010, a total of around 17,000 HIV/AIDS patients in medical care has been recorded, of which 826 were new HIV diagnosed patients. The proportion of MSM among the newly diagnosed slightly increased from 66% in 2010 to 68% in 2011.
The urgent need to accelerate the development of an AIDS vaccine prompted the United Nations Programme on HIV/AIDS (UNAIDS) and the 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 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 a vaccine against HIV is potentially feasible. Other vaccine candidates from different manufacturers are currently being tested in phase I or II clinical trials.

6.4 Hepatitis C

Hepatitis C is a liver disease caused by the hepatitis C virus (HCV). The disease can range in severity from a mild illness lasting a few weeks to a serious, lifelong condition which can lead to cirrhosis of the liver, liver failure or liver cancer. HCV is globally distributed and it is estimated that up to 170 million people (3% of the world's population) are infected worldwide; more than 350,000 people die every year from hepatitis C-related liver diseases. About 75-85% of newly infected persons develop chronic disease and 60–70% of chronically infected people develop chronic liver disease; 5–20% develop cirrhosis and 1–5% die from cirrhosis or liver cancer. In 25% of liver cancer patients, the underlying cause is hepatitis C. The hepatitis C virus is transmitted through contact with the blood of an infected person [260]. 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 who received blood transfusions before the screening of infected blood products and intravenous drug users. In The Netherlands, the number of registered acute hepatitis C infections was 62 in 2011, which means a doubling compared with 2010.

A vaccine which 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 under 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 seen in HIV. Other factors which 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 Clostridium difficile

Clostridium difficile (CD) is a major public health concern in Europe and North America. *C. difficile* bacterium can be found in 80% of all infants and 9% of all adults but rarely causes infections in healthy persons. However, it 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. Disease is caused by the production of toxins, most notably toxin A and B. 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, the results of 18 hospitals participating in the sentinel surveillance revealed the mean incidence of CDI is 15 per 10,000 admissions, varying from 3 to 29 per 10,000 admissions for the period May 2011 to May 2012 [261]. Extrapolating the data of sentinel surveillance to all hospitals in the Netherlands, it is estimated that more than 2700 hospitalised patients annually will develop CDI of which 100 will succumb attributable or contributable to CDI. In these estimations, the impact of CDI in other healthcare facilities than hospitals was not included. Therefore, the true number of patients with CDI admitted to healthcare facilities will be higher.
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.

6.6 Staphylococcus aureus

Staphylococcus aureus is a bacterium which commonly colonises human skin and mucosa (e.g. inside the nose) without causing any problems. It can also cause disease, particularly if there is an opportunity for the bacteria to enter the body, for example through broken skin or a medical procedure. 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 of MRSA in hospitals is 1% and in the general population 0.13%, which is low compared with other EU countries. MRSA is responsible for several difficult-to-treat infections in humans since the bacterium is resistant to a large group of antibiotics, including the beta lactams (i.e. penicillines, flucloxacilline and cephalosporines). MRSA is one of the leading causes of nosocomial pneumonia and surgical site infection and the second leading cause of nosocomial blood stream infections. In 2010, 1.6% of the aureus-isolates in the Netherlands was an MRSA, which is equal to the percentage in 2009 (RIVM). The Netherlands, Norway and Sweden have the lowest MRSA-prevalence within Europe. Transmission in hospitals hardly ever occurs, invasive infections are rare.
Several companies (Sanofi-Pasteur together with Intercell; Pfizer; Novartis) 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 the vaccine elicited a positive immune response to each of the three components.

6.7 Pseudomonas aeruginosa

Most serious *Pseudomonas aeruginosa* infections occur in hospitalised and critically or chronically ill patients. *P. aeruginosa* infections primarily affect 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).

6.8 Group B Streptococcus

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 a compromised immune system. Group B Streptococcus is part of the normal flora of the gut and genital tract and is found in 20-40% of women. Carriage of the organism is asymptomatic. 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 [262]. 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 infant. Infection with 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. Newborn GBS disease is separated into early-onset disease occurring on living days 0–7 and late-onset disease which starts somewhere between days 7 and 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.

6.9 Cytomegalovirus

Cytomegalovirus (CMV) causes a spectrum of disease syndromes in children and adults. CMV is a cause of mononucleosis in immunocompetent individuals and 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 Europe and the United States, 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. The RIVM is currently performing a study in collaboration with Leiden University Medical Center (LUMC) on the disease burden of congenital CMV infections in the Netherlands (Crocus study).
GSK, Sanofi Pasteur and Novartis in collaboration with Alphafax are developing prophylactic vaccines to prevent congenital CMV infection. These vaccines are in early clinical development and are likely to be targeted to adolescent females prior to their first pregnancy. Dempsey et al. assessed the cost-effectiveness of CMV vaccination to this target group in the United States [263]. Both maternal outcomes related to vaccination, and infant outcomes related to congenital CMV infection were included in the study. Dempsey found vaccinating all adolescent females against cytomegalovirus would be both less costly and with greater clinical benefits than not vaccinating. Among a population of 100,000 adolescent females, the vaccination strategy cost $ 32.3 million dollars less than not vaccinating, and avoided substantial numbers of infants affected with hearing loss, vision loss, and mental retardation, and eight infant deaths. The model was most sensitive to variations in vaccine efficacy. When vaccine efficacy against disease was less than 61%, not vaccinating became the preferred strategy because it was less expensive than vaccinating, without substantial changes in clinical benefits to the population. In conclusion, universal vaccination of adolescent females to protect their future children against congenital CMV infection is likely to be cost-effective if CMV vaccines could achieve at least a 61% reduction in the incidence of CMV disease in neonates.

6.10 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 noroviruses (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. In a recent live norovirus challenge study in adult volunteers, the dry powder vaccine candidate met all of its primary endpoints, including statistically significant reductions in illness, infection and severity of illness. These results confirm for the first time that norovirus illness can be prevented by vaccination (Ligocyte Pharmaceuticals website). However, since noroviruses are a heterogeneous group and, more significantly, evolve even more rapidly every season than influenza viruses, it is anticipated a norovirus vaccine will have to be reformulated frequently, perhaps yearly, as is the case for influenza seasonal vaccine.

6.11 Others

Vaccines in development but currently 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. Recently published data with Sanofi’s Dengue virus vaccine generated an antibody response for all four

dengue virus types, but evidence of protection was only demonstrated against three of the four strains circulating in Thailand. The problem with dengue is that an infection with one strain usually results in mild disease but a subsequent infection with a second strain results in more severe dengue fever, indicating a vaccine should provide protection to all strains.
An ongoing phase 3 study of the efficacy, safety, and immunogenicity of candidate malaria vaccine RTS,S/AS01 shows an efficacy of 50.4% (95% confidence interval (CI), 45.8 to 54.6) in the intention-to-treat population and 55.8% (97.5% CI, 50.6 to 60.4) in the per-protocol population,
For Japanese encephalitis vaccines made in China and Japan are available.
A West Nile virus vaccine development programme has been put on hold, despite a large disease outbreak in the US, due to a difficult phase III design.
In case disease incidences increases in the Netherlands, vaccines against these diseased will be evaluated for introduction in the NIP.

References

1. Brandsema P, Dijkstra F, Euser S, van Gageldonk-Lafeber A, de Lange M, Meijer A, et al. Annual report surveillance respiratory infectious diseases. Bilthoven: RIVM; 2012. RIVM Report 201041001.
2. Jansen B, Tacken M, Mulder J, Visscher S, Schlief A, Tiersma W, et al. Monitoring Nationaal Programma Griepppreventie 2011. Nijmegen: LINH, IQ healthcare; 2011.
3. RIVM. Voor wie is de jaarlijkse griepprik? 2009; Available from: www.rivm.nl/griepprik/voor_wie/.
4. KNCV Tuberculosefonds. 'Tuberculose in Nederland 2010', Surveillancerapport over de tuberculosesituatie in Nederland. Manuel. The Hague: KNCV Tuberculosefonds; 2011 Contract No. 978-90-77865-00-2.
5. Dutch Health Council. The National Immunisation Programme in the Dutch Caribbean. Den Haag: Dutch Health Council; 2012 Contract No. 2012/13.
6. van Vliet H. Geschiedenis van meldingsplicht. Tijdschrift voor infectieziekten. 2009;4(2):51-60.
7. de Melker HE, Conyn-van Spaendonck MAE, Sprenger MJ. Infectieziekten in Nederland: epidemiologie, diagnostiek en bestrijding. The Hague: RIVM; 1997.
8. de Greeff S, Spanjaard L, Dankert J, Hoebe C, Nagelkerke N, de Melker H. Underreporting of Meningococcal Disease Incidence in the Netherlands: Results from a Capture–Recapture Analysis Based on Three Registration Sources with Correction for False Positive Diagnoses. European Journal of Epidemiology. 2006;21(4):315-21.
9. van den Hof S, Conyn-van Spaendonck M, de Melker HE, Geubbels E, Suijkerbuijk AWM, Talsma E, et al. The effects of vaccination, the incidence of target diseases. Bilthoven: RIVM; 1998. RIVM Report 213676008.
10. Sprenger MJ, Van Pelt W. Infectieziekten Surveillance en Informatie Systeem. Bilthoven: RIVM; 1994. RIVM Report 214670001.
11. De Melker HE, Conyn-van Spaendonck MA. Immunosurveillance and the evaluation of national immunization programmes: a population-based approach. Epidemiol Infect. 1998;121(3):637-43.
12. van der Klis FR, Mollema L, Berbers GA, de Melker HE, Coutinho RA. Second national serum bank for population-based seroprevalence studies in the Netherlands. Neth J Med. 2009;67(7):301-8.
13. van Lier A, Oomen P, de Hoogh P, Drijfhout I, Elsinghorst B, Kemmeren J, et al. Praeventis, the immunisation register of the Netherlands: a tool to evaluate the National Immunisation Programme. Euro Surveill. 2012;17(17).
14. Vermeer-de Bondt PE, Phaff TAJ, Moorer-Lanser N, van der Maas NAT. Adverse events following immunization under the National Vaccination Programme of the Netherlands. Number XVII-reports in 2010: RIVM; 2011. RIVM Report 205051004.
15. van Lier A, Oomen PJ, Giesbers H, Drijfhout IH, de Hoogh PAAM, de Melker HE. Vaccinatiegraad Rijksvaccinatieprogramma Nederland: Verslagjaar 2012. Bilthoven: RIVM; 2012. RIVM Report 201001001.
16. Harmsen I, Mollema L, Ruiter R, Paulussen T, de Melker H, Kok G. Why parents refuse childhood vaccination: a qualitative study with the use of online focus groups. Submitted. 2012.
17. Harmsen I, Ruiter R, Paulussen T, Mollema L, Kok G, de Melker H. Factors that influence vaccination decision making by parents who visit an anthroposophical child welfare center: a focus groups study. Adv Prev Med. 2012;2012:175694.

18. Bos H, Harmsen I, Mollema L, de Melker H. Factors that influence decision-making about childhood vaccination among parents of different ethnic backgrounds in the Netherlands; a qualitative assessment using focus groups. Manuscript Msc thesis. 2012.
19. Hirobe S, Matsuo K, Quan YS, Kamiyama F, Morito H, Asada H, et al. Clinical study of transcutaneous vaccination using a hydrogel patch for tetanus and diphtheria. Vaccine. 2012;30(10):1847-54.
20. De Melker HE, Conyn-van Spaendonck MA, Rumke HC, van Wijngaarden JK, Mooi FR, Schellekens JF. Pertussis in The Netherlands: an outbreak despite high levels of immunization with whole-cell vaccine. Emerg Infect Dis. 1997;3(2):175-8.
21. Van 't Klooster TM, De Melker H. The National Immunization Programme in the Netherlands; developments in 2011. Bilthoven: National Institute for Public Health and the Environment; 2011. RIVM Report 210021015.
22. Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med. 2012;367(11):1012-9.
23. Witt MA, Katz PH, Witt DJ. Unexpectedly limited durability of immunity following acellular pertussis vaccination in preadolescents in a North American outbreak. Clin Infect Dis. 2012;54(12):1730-5.
24. Westra TA, de Vries R, Tamminga JJ, Sauboin CJ, Postma MJ. Cost-effectiveness analysis of various pertussis vaccination strategies primarily aimed at protecting infants in the Netherlands. Clin Ther. 2010;32(8):1479-95.
25. Rozenbaum MH, De Cao E, Postma MJ. Cost-effectiveness of pertussis booster vaccination in the Netherlands. Vaccine. 2012;30(50):7327-31.
26. Greer AL, Fisman DN. Use of models to identify cost-effective interventions: pertussis vaccination for pediatric health care workers. Pediatrics. 2011;128(3):e591-9.
27. Mooi FR, van Loo IH, van Gent M, He Q, Bart MJ, Heuvelman KJ, et al. Bordetella pertussis strains with increased toxin production associated with pertussis resurgence. Emerg Infect Dis. 2009;15(8):1206-13.
28. Advani A, Gustafsson L, Carlsson RM, Donnelly D, Hallander HO. Clinical outcome of pertussis in Sweden: association with pulsed-field gel electrophoresis profiles and serotype. APMIS. 2007;115(6):736-42.
29. Carbonetti NH, Artamonova GV, Van Rooijen N, Ayala VI. Pertussis toxin targets airway macrophages to promote Bordetella pertussis infection of the respiratory tract. Infect Immun. 2007;75(4):1713-20.
30. Kirimanjeswara GS, Agosto LM, Kennett MJ, Bjornstad ON, Harvill ET. Pertussis toxin inhibits neutrophil recruitment to delay antibody-mediated clearance of Bordetella pertussis. J Clin Invest. 2005;115(12):3594-601.
31. Mooi FR. Bordetella pertussis and vaccination: the persistence of a genetically monomorphic pathogen. Infect Genet Evol. 2010;10(1):36-49.
32. Bouchez V, Brun D, Cantinelli T, Dore G, Njamkepo E, Guiso N. First report and detailed characterization of B. pertussis isolates not expressing Pertussis Toxin or Pertactin. Vaccine. 2009;27(43):6034-41.
33. Otsuka N, Kamachi K, Han H, Toyoizumi-Ajisaka H, Nakamura Y, Arakawa Y. Prevalence and genetic characterization of pertactin-deficient Bordetella pertussis isolates in Japan. Ninth International Bordetella Symposium; Baltimore2010.
34. Nederlands Bijwerkingen Centrum Lareb. Rapportage gemelde bijwerkingen na vaccinaties in het Rijksvaccinatieprogramma 2011. 's-Hertogenbosch: http://www.lareb.nl/getmedia/7fa50d1a-01d9-47b9-beb5-2ea55e79d809/Lareb-rapportage-RVP-2011.pdf.
35. Chatterjee A, O'Keefe C, Varman M, Klein NP, Luber S, Tomovici A, et al. Comparative immunogenicity and safety of different multivalent component

pertussis vaccine formulations and a 5-component acellular pertussis vaccine in infants and toddlers: a randomized, controlled, open-label, multicenter study. Vaccine. 2012;30(23):3360-8.
36. Dutta AK, Verghese VP, Pemde H, Mathew LG, Ortiz E. Immunogenicity and Safety of a DTaP-IPV//PRP~T Vaccine (Pentaxim) Booster Dose During the Second Year of Life in Indian Children Primed with the Same Vaccine. Indian Pediatr. 2012;49(10):793-8.
37. Madhi SA, Cutland C, Jones S, Groome M, Ortiz E. One-year post-primary antibody persistence and booster immune response to a DTaP-IPV//PRP~T vaccine (Pentaxim) given at 18 - 19 months of age in South African children primed at 6, 10 and 14 weeks of age with the same vaccine. S Afr Med J. 2011;101(12):879-83.
38. Li RC, Li FX, Li YP, Hou QM, Li CG, Li YN, et al. Antibody persistence at 18-20 months of age and safety and immunogenicity of a booster dose of a combined DTaP-IPV//PRP approximately T vaccine compared to separate vaccines (DTaP, PRP approximately T and IPV) following primary vaccination of healthy infants in the People's Republic of China. Vaccine. 2011;29(50):9337-44.
39. Aquino AG, Brito MG, Doniz CE, Herrera JF, Macias M, Zambrano B, et al. A fully liquid DTaP-IPV-Hep B-PRP-T hexavalent vaccine for primary and booster vaccination of healthy Mexican children. Vaccine. 2012;30(45):6492-500.
40. Macias M, Lanata CF, Zambrano B, Gil AI, Amemiya I, Mispireta M, et al. Safety and Immunogenicity of an Investigational Fully Liquid Hexavalent DTaP-IPV-Hep B-PRP-T Vaccine at Two, Four and Six Months of Age Compared With Licensed Vaccines in Latin America. Pediatr Infect Dis J. 2012;31(8):e126-32.
41. Tregnaghi M, Zambrano B, Santos-Lima E. Antibody persistence after a primary series of a new DTaP-IPV-Hep B-PRP-T combined vaccine or separate DTaP-IPV//PRP-T and hepatitis B vaccines at 2, 4, and 6 months of age and the effect of a subsequent DTaP-IPV//PRP-T booster vaccination at 18 months of age in healthy Argentinean infants. Pediatr Infect Dis J. 2012;31(1):e24-30.
42. Van Der Meeren O, Kuriyakose S, Kolhe D, Hardt K. Immunogenicity of Infanrix hexa administered at 3, 5 and 11 months of age. Vaccine. 2012;30(17):2710-4.
43. Berner R, Boisnard F, Thomas S, Mwawasi G, Reynolds D. Safety and immunogenicity of fully liquid DTaP(5)-IPV-Hib pediatric combination vaccine (Pediacel((R))) compared to DTaP(3)-HBV-IPV/Hib (Infanrix((R)) Hexa) when coadministered with heptavalent pneumococcal conjugate vaccine (PCV7) as a booster at 11-18 months of age: A phase III, modified double-blind, randomized, controlled, multicenter study. Vaccine. 2012;30(35):5270-7.
44. Grimprel E, Wysocki J, Boisnard F, Thomas S, Mwawasi G, Reynolds D. Immunogenicity and safety of fully liquid DTaP(5)-IPV-Hib compared with DTaP(3)-IPV/Hib when both coadministered with a heptavalent pneumococcal conjugate vaccine (PCV7) at 2, 3, 4, and 12 to 18 months of age: a phase III, single-blind, randomised, controlled, multicentre study. Vaccine. 2011;29(43):7370-8.
45. Ferrera G, Cuccia M, Mereu G, Icardi G, Bona G, Esposito S, et al. Booster vaccination of pre-school children with reduced-antigen-content diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine co-administered with measles-mumps-rubella-varicella vaccine: A randomized, controlled trial in children primed according to a 2+1 schedule in infancy. Hum Vaccin Immunother. 2012;8(3).
46. Klein NP, Weston WM, Kuriyakose S, Kolhe D, Howe B, Friedland LR, et al. An open-label, randomized, multi-center study of the immunogenicity and safety of DTaP-IPV (Kinrix) co-administered with MMR vaccine with or without

varicella vaccine in healthy pre-school age children. Vaccine. 2012;30(3):668-74.
47. Langley JM, Halperin SA, Rubin E, White C, McNeil S, Mutch J, et al. Safety and immunogenicity of 2 mixed primary infant immunization schedules of pentavalent diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, and Haemophilus influenzae Type B vaccines at 2, 4, and 6 months of age: a randomized controlled trial. Pediatr Infect Dis J. 2012;31(2):189-92.
48. Halperin BA, Morris A, Mackinnon-Cameron D, Mutch J, Langley JM, McNeil SA, et al. Kinetics of the antibody response to tetanus-diphtheria-acellular pertussis vaccine in women of childbearing age and postpartum women. Clin Infect Dis. 2011;53(9):885-92.
49. Thierry-Carstensen B, Jordan K, Uhlving HH, Dalby T, Sorensen C, Jensen AM, et al. A randomised, double-blind, non-inferiority clinical trial on the safety and immunogenicity of a tetanus, diphtheria and monocomponent acellular pertussis (TdaP) vaccine in comparison to a tetanus and diphtheria (Td) vaccine when given as booster vaccinations to healthy adults. Vaccine. 2012;30(37):5464-71.
50. Weston WM, Friedland LR, Wu X, Howe B. Vaccination of adults 65 years of age and older with tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Boostrix((R))): Results of two randomized trials. Vaccine. 2011;30(9):1721-8.
51. Zheteyeva YA, Moro PL, Tepper NK, Rasmussen SA, Barash FE, Revzina NV, et al. Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women. Am J Obstet Gynecol. 2012;207(1):59 e1-7.
52. Moro PL, Yue X, Lewis P, Haber P, Broder K. Adverse events after tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine administered to adults 65 years of age and older reported to the Vaccine Adverse Event Reporting System (VAERS), 2005-2010. Vaccine. 2011;29(50):9404-8.
53. Sharma H, Patil V, Sharma D, Kapre S, Jadhav S, Ravetkar S, et al. A phase III, randomized controlled study to assess the safety and immunogenicity of a semi-synthetic diphtheria, tetanus and whole-cell pertussis vaccine in Indian infants. Vaccine. 2012;30(43):6157-62.
54. Hendrikx LH, Schure RM, Ozturk K, de Rond LG, de Greeff SC, Sanders EA, et al. Different IgG-subclass distributions after whole-cell and acellular pertussis infant primary vaccinations in healthy and pertussis infected children. Vaccine. 2011;29(40):6874-80.
55. Poulter LW, Seymour GJ, Duke O, Janossy G, Panayi G. Immunohistological analysis of delayed-type hypersensitivity in man. Cell Immunol. 1982;74(2):358-69.
56. Quinn P, Gold M, Royle J, Buttery J, Richmond P, McIntyre P, et al. Recurrence of extensive injection site reactions following DTPa or dTpa vaccine in children 4-6 years old. Vaccine. 2011;29(25):4230-7.
57. Rowe J, Yerkovich ST, Richmond P, Suriyaarachchi D, Fisher E, Feddema L, et al. Th2-associated local reactions to the acellular diphtheria-tetanus-pertussis vaccine in 4- to 6-year-old children. Infect Immun. 2005;73(12):8130-5.
58. Kemmeren JM, Timmer SS, van der Maas NA, de Melker HE. Comparison of the tolerability of an acellular pertussis-containing vaccine given as the fifth booster dose in differently primed children. Vaccine. 2011;29(26):4373-7.
59. Zhang L, Prietsch SO, Axelsson I, Halperin SA. Acellular vaccines for preventing whooping cough in children. Cochrane Database Syst Rev. 2011(1):CD001478.

60. Whooping cough vaccination; coverage may be widened. Br Med J (Clin Res Ed). 2012;345(7868):E5201.
61. Pertussis epidemic - Washington, 2012. MMWR Morb Mortal Wkly Rep. 2012;61:517-22.
62. Locht C, Mielcarek N. New pertussis vaccination approaches: en route to protect newborns? FEMS Immunol Med Microbiol. 2012;66(2):121-33.
63. Wendelboe AM, Van Rie A, Salmaso S, Englund JA. Duration of immunity against pertussis after natural infection or vaccination. Pediatr Infect Dis J. 2005;24(5 Suppl):S58-61.
64. Feunou PF, Kammoun H, Debrie AS, Mielcarek N, Locht C. Long-term immunity against pertussis induced by a single nasal administration of live attenuated B. pertussis BPZE1. Vaccine. 2010;28(43):7047-53.
65. Feunou PF, Bertout J, Locht C. T- and B-cell-mediated protection induced by novel, live attenuated pertussis vaccine in mice. Cross protection against parapertussis. PLoS One. 2010;5(4):e10178.
66. Stubbe M, Mortelmans LJ, Desruelles D, Swinnen R, Vranckx M, Brasseur E, et al. Improving tetanus prophylaxis in the emergency department: a prospective, double-blind cost-effectiveness study. Emerg Med J. 2007;24(9):648-53.
67. McVicar J. Should we test for tetanus immunity in all emergency department patients with wounds? Emerg Med J. 2012. [Epub ahead of print].
68. Savolainen C, Hovi T. Caveat: poliovirus may be hiding under other labels. Lancet. 2003;361(9364):1145-6.
69. Cadorna-Carlos J, Vidor E, Bonnet MC. Randomized controlled study of fractional doses of inactivated poliovirus vaccine administered intradermally with a needle in the Philippines. Int J Infect Dis. 2012;16(2):e110-6.
70. Quiambao B, Van Der Meeren O, Kolhe D, Gatchalian S. A randomized, dose-ranging assessment of the immunogenicity and safety of a booster dose of a combined diphtheria-tetanus-whole cell pertussis-hepatitis B-inactivated poliovirus-Hemophilus influenzae type b (DTPw-HBV-IPV/Hib) vaccine vs. co-administration of DTPw-HBV/Hib and IPV vaccines in 12 to 24 months old Filipino toddlers. Hum Vaccin Immunother. 2012;8(3):347-54.
71. Kersten G, Hazendonk T, Beuvery C. Antigenic and immunogenic properties of inactivated polio vaccine made from Sabin strains. Vaccine. 1999;17(15-16):2059-66.
72. Bruce Aylward R, Sutter RW, Cochi SL, Thompson KM, Jafari H, Heymann D. Risk management in a polio-free world. Risk Anal. 2006;26(6):1441-8.
73. Heymann DL, Sutter RW, Aylward RB. A global call for new polio vaccines. Nature. 2005;434(7034):699-700.
74. Bakker WA, Thomassen YE, Van't Oever AG, Westdijk J, van Oijen MG, Sundermann LC, et al. Inactivated polio vaccine development for technology transfer using attenuated Sabin poliovirus strains to shift from Salk-IPV to Sabin-IPV. Vaccine. 2011;29(41):7188-96.
75. Westdijk J, Brugmans D, Martin J, van't Oever A, Bakker WA, Levels L, et al. Characterization and standardization of Sabin based inactivated polio vaccine: proposal for a new antigen unit for inactivated polio vaccines. Vaccine. 2011;29(18):3390-7.
76. Verdijk P, Rots NY, Bakker WA. Clinical development of a novel inactivated poliomyelitis vaccine based on attenuated Sabin poliovirus strains. Expert Rev Vaccines. 2011;10(5):635-44.
77. Knol M.J., Spijkerman J., Veenhoven R.H., Elberse K.E., van Gageldonk P.G.M., Wijmenga-Monsuur A.J., et al. The PIM study: Immunogenicity of the 13-valent polysaccharide pneumococcal conjugate vaccine. Comparison of

current schedule with alternative and reduced immunisation schedules. Bilthoven: RIVM; 2012. RIVM Report 230182001.
78. Van Borden J., Hahné S., Rogmans B. Doof door bof. Medisch Contact 2012, nr 29/30.
79. Opstelten W, Hahne SJ, van Roijen JH, van Paridon L, Wolters B, Swaan CM. [Mumps makes a comeback]. Ned Tijdschr Geneeskd. 2012;156(43):A5187.
80. Fanoy EB, Cremer J, Ferreira JA, Dittrich S, van Lier A, Hahne SJ, et al. Transmission of mumps virus from mumps-vaccinated individuals to close contacts. Vaccine. 2011;29(51):9551-6.
81. Dittrich S, Hahne S, van Lier A, Kohl R, Boot H, Koopmans M, et al. Assessment of serological evidence for mumps virus infection in vaccinated children. Vaccine. 2011;29(49):9271-5.
82. Snijders BE, van Lier A, van de Kassteele J, Fanoy EB, Ruijs WL, Hulshof F, et al. Mumps vaccine effectiveness in primary schools and households, the Netherlands, 2008. Vaccine. 2012;30(19):2999-3002.
83. Wielders CC, van Binnendijk RS, Snijders BE, Tipples GA, Cremer J, Fanoy E, et al. Mumps epidemic in orthodox religious low-vaccination communities in the Netherlands and Canada, 2007 to 2009. Euro Surveill. 2011;16(41).
84. Eriksen J, Davidkin I, Kafatos G, Andrews N, Barbara C, Cohen D, et al. Seroepidemiology of mumps in Europe (1996-2008): why do outbreaks occur in highly vaccinated populations? Epidemiol Infect. 2012:1-16. [Epub ahead of print].
85. van den Hoek A, Sonder GJ, Scholing M, Gijselaar D, van Binnendijk RS. Two cases of mild IgM-negative measles in previously vaccinated adults, the Netherlands, April and July 2011. Euro Surveill. 2011;16(48).
86. Mankertz A, Mihneva Z, Gold H, Baumgarte S, Baillot A, Helble R, et al. Spread of measles virus D4-Hamburg, Europe, 2008-2011. Emerg Infect Dis. 2011;17(8):1396-401.
87. Cheng DR, Crawford NW, Hayman M, Buckley C, Buttery JP. Recurrent 6th nerve palsy in a child following different live attenuated vaccines: case report. BMC Infect Dis. 2012;12:105.
88. Wilson K, Hawken S, Kwong JC, Deeks S, Crowcroft NS, Van Walraven C, et al. Adverse events following 12 and 18 month vaccinations: a population-based, self-controlled case series analysis. PLoS One. 2011;6(12):e27897.
89. Demicheli V, Rivetti A, Debalini MG, Di Pietrantonj C. Vaccines for measles, mumps and rubella in children. Cochrane Database Syst Rev. 2012;2:CD004407.
90. Leonardi M, Bromberg K, Baxter R, Gardner JL, Klopfer S, Nicholson O, et al. Immunogenicity and safety of MMRV and PCV-7 administered concomitantly in healthy children. Pediatrics. 2011;128(6):e1387-94.
91. Blatter MM, Klein NP, Shepard JS, Leonardi M, Shapiro S, Schear M, et al. Immunogenicity and safety of two tetravalent (measles, mumps, rubella, varicella) vaccines coadministered with hepatitis A and pneumococcal conjugate vaccines to children twelve to fourteen months of age. Pediatr Infect Dis J. 2012;31(8):e133-40.
92. Diaz-Ortega JL, Bennett JV, Castaneda D, Martinez D, Fernandez de Castro J. Aerosolized MMR vaccine: evaluating potential transmission of components to vaccine administrators and contacts of vaccinees. Biologicals. 2012;40(4):278-81.
93. De Serres G, Boulianne N, Defay F, Brousseau N, Benoit M, Lacoursiere S, et al. Higher risk of measles when the first dose of a 2-dose schedule of measles vaccine is given at 12-14 months versus 15 months of age. Clin Infect Dis. 2012;55(3):394-402.

94. Bonacic Marinovic AA, Swaan C, Wichmann O, van Steenbergen J, Kretzschmar M. Effectiveness and timing of vaccination during school measles outbreak. Emerg Infect Dis. 2012;18(9):1405-13.
95. ECDC. Measles cases by month, 2011. http://ecdc.europa.eu/en/healthtopics/measles/epidemiological_data/measles_cases/Pages/data_bymonth.aspx. Accessed 23 October 2012.
96. WHO Geneva. Global Measles and Rubella Strategic Plan 2012-2020. Available from: http://whqlibdoc.who.int/publications/2012/9789241503396_eng.pdf.
97. WHO Euro. Epidemiological brief 21. Available from: http://www.euro.who.int/__data/assets/pdf_file/0004/159475/WHO_EPI_Brief_Feb_2012e.pdf.
98. Nederlands Bijwerkingen Centrum Lareb. Rapportage gemelde bijwerkingen na vaccinaties in het Rijksvaccinatieprogramma 2011. 's-Hertogenbosch: Lareb; 2012.
99. McVernon J, Nolan T, Richmond P, Reynolds G, Nissen M, Lambert SB, et al. A randomized trial to assess safety and immunogenicity of alternative formulations of a quadrivalent meningococcal (A, C, Y, and W-135) tetanus protein conjugate vaccine in toddlers. Pediatr Infect Dis J. 2012;31(1):e15-23.
100. Dbaibo G, Macalalad N, Reyes MR, Dimaano E, Bianco V, Baine Y, et al. The immunogenicity and safety of an investigational meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine (ACWY-TT) compared with a licensed meningococcal tetravalent polysaccharide vaccine: A randomized, controlled non-inferiority study. Hum Vaccin Immunother. 2012;8(7):873-80.
101. Ostergaard L, Silfverdal SA, Berglund J, Flodmark CE, West C, Bianco V, et al. A tetravalent meningococcal serogroups A, C, W-135, and Y tetanus toxoid conjugate vaccine is immunogenic and well-tolerated when co-administered with Twinrix((R)) in subjects aged 11-17 years: an open, randomised, controlled trial. Vaccine. 2012;30(4):774-83.
102. Pina LM, Bassily E, Machmer A, Hou V, Reinhardt A. Safety and Immunogenicity of a Quadrivalent Meningococcal Polysaccharide Diphtheria-Toxoid-Conjugate Vaccine in Infants and Toddlers: Three Multicenter Phase III Studies. Pediatr Infect Dis J. 2012.
103. Siberry GK, Warshaw MG, Williams PL, Spector SA, Decker MD, Jean-Philippe P, et al. Safety and immunogenicity of quadrivalent meningococcal conjugate vaccine in 2- to 10-year-old human immunodeficiency virus-infected children. Pediatr Infect Dis J. 2012;31(11):1173-83.
104. Omenaca F, Aristegui J, Tejedor JC, Moreno-Perez D, Ruiz-Contreras J, Merino JM, et al. Combined Haemophilus Influenzae type B-Neisseria meningitidis serogroup C vaccine is immunogenic and well tolerated in preterm infants when coadministered with other routinely recommended vaccines. Pediatr Infect Dis J. 2011;30(11):e216-24.
105. Bryant K, McVernon J, Marchant C, Nolan T, Marshall G, Richmond P, et al. Immunogenicity and safety of measles-mumps-rubella and varicella vaccines coadministered with a fourth dose of Haemophilus influenzae type b and Neisseria meningitidis serogroups C and Y-tetanus toxoid conjugate vaccine in toddlers: A pooled analysis of randomized trials. Hum Vaccin Immunother. 2012;8(8):1036-41.
106. Klein NP, Shepard J, Bedell L, Odrljin T, Dull P. Immunogenicity and safety of a quadrivalent meningococcal conjugate vaccine administered concomitantly with measles, mumps, rubella, varicella vaccine in healthy toddlers. Vaccine. 2012;30(26):3929-36.
107. Kaaijk P, van der Ende A, Berbers G, van den Dobbelsteen GP, Rots NY. Is a single dose of meningococcal serogroup C conjugate vaccine sufficient for protection? Experience from the Netherlands. BMC Infect Dis. 2012;12:35.

108. Snape MD, Kelly DF, Salt P, Green S, Snowden C, Diggle L, et al. Serogroup C meningococcal glycoconjugate vaccine in adolescents: persistence of bactericidal antibodies and kinetics of the immune response to a booster vaccine more than 3 years after immunization. Clin Infect Dis. 2006;43(11):1387-94.
109. De Voer RM, Mollema L, Schepp RM, de Greeff SC, van Gageldonk PG, de Melker HE, et al. Immunity against Neisseria meningitidis serogroup C in the Dutch population before and after introduction of the meningococcal c conjugate vaccine. PLoS One. 2010;5(8):e12144.
110. De Voer RM, van der Klis FR, Engels CW, Schepp RM, van de Kassteele J, Sanders EA, et al. Kinetics of antibody responses after primary immunization with meningococcal serogroup C conjugate vaccine or secondary immunization with either conjugate or polysaccharide vaccine in adults. Vaccine. 2009;27(50):6974-82.
111. Koedijk F, van der Sande M, Hahné S. acute hepatitis B in 2010. Infectieziekten Bulletin.2011;22(10):366-9.
112. Whelan J, Sonder G, Heuker J, van den Hoek A. Incidence of acute hepatitis B in different ethnic groups in a low-endemic country, 1992-2009: increased risk in second generation migrants. Vaccine. 2012;30(38):5651-5.
113. Veldhuijzen IK, Wolter R, Rijckborst V, Mostert M, Voeten HA, Cheung Y, et al. Identification and treatment of chronic hepatitis B in Chinese migrants: Results of a project offering on-site testing in Rotterdam, The Netherlands. J Hepatol. 2012;57(6):111-6.
114. Richter C, Beest GT, Sancak I, Aydinly R, Bulbul K, Laetemia-Tomata F, et al. Hepatitis B prevalence in the Turkish population of Arnhem: implications for national screening policy? Epidemiol Infect. 2012;140(4):724-30.
115. Veldhuijzen IK, Toy M, Hahne SJ, De Wit GA, Schalm SW, de Man RA, et al. Screening and early treatment of migrants for chronic hepatitis B virus infection is cost-effective. Gastroenterology. 2010;138(2):522-30.
116. Ray P, Black S, Shinefield H, Dillon A, Carpenter D, Lewis E, et al. Risk of rheumatoid arthritis following vaccination with tetanus, influenza and hepatitis B vaccines among persons 15-59 years of age. Vaccine. 2011;29(38):6592-7.
117. Hernandez-Bernal F, Aguilar-Betancourt A, Aljovin V, Arias G, Valenzuela C, de Alejo KP, et al. Comparison of four recombinant hepatitis B vaccines applied on an accelerated schedule in healthy adults. Hum Vaccin. 2011;7(10):1026-36.
118. Lee AW, Vesikari T, Gilbert CL, Klopfer SO, Schodel FP, Bhuyan PK. Immunogenicity and safety of a Haemophilus influenzae B (Hib)-hepatitis B vaccine with a modified process hepatitis B component administered with concomitant pneumococcal conjugate vaccine to infants. Vaccine. 2011;29(45):7942-8.
119. Romano L, Zanetti AR. Safety and immunogenicity of a recombinant hepatitis B vaccine manufactured by a modified process in healthy infants. Expert Rev Vaccines. 2011;10(9):1261-4.
120. Minervini G, McCarson BJ, Reisinger KS, Martin JC, Stek JE, Atkins BM, et al. Safety and immunogenicity of a modified process hepatitis B vaccine in healthy neonates. Vaccine. 2012;30(8):1476-80.
121. Gilbert CL, Klopfer SO, Martin JC, Schodel FP, Bhuyan PK. Safety and immunogenicity of a modified process hepatitis B vaccine in healthy adults >/=50 years. Hum Vaccin. 2011;7(12):1336-42.
122. Sablan BP, Kim DJ, Barzaga NG, Chow WC, Cho M, Ahn SH, et al. Demonstration of safety and enhanced seroprotection against hepatitis B with investigational HBsAg-1018 ISS vaccine compared to a licensed hepatitis B vaccine. Vaccine. 2012;30(16):2689-96.

123. Halperin SA, McNeil S, Langley JM, Smith B, MacKinnon-Cameron D, McCall-Sani R, et al. Safety and immunogenicity of different two-dose regimens of an investigational hepatitis B vaccine (hepatitis B surface antigen co-administered with an immunostimulatory phosphorothioate oligodeoxyribonucleotide) in healthy young adults. Vaccine. 2012;30(36):5445-8.
124. Halperin SA, Ward B, Cooper C, Predy G, Diaz-Mitoma F, Dionne M, et al. Comparison of safety and immunogenicity of two doses of investigational hepatitis B virus surface antigen co-administered with an immunostimulatory phosphorothioate oligodeoxyribonucleotide and three doses of a licensed hepatitis B vaccine in healthy adults 18-55 years of age. Vaccine. 2012;30(15):2556-63.
125. Xiridou M, van Houdt R, Hahné S, van Steenbergen J, Coutinho R, Kretzschmar M. The impact of risk group vaccination against hepatitis B virus among men who have sex with men. Annual Meeting of the European Society for Clinical Virology, Madrid, 4-7 September 2012.Poster No P-016.
126. Liakou CD, Askiti V, Mitsioni A, Stefanidis CJ, Theodoridou MC, Spoulou VI. Safety, immunogenicity and kinetics of immune response to 7-valent pneumococcal conjugate vaccine in children with idiopathic nephrotic syndrome. Vaccine. 2011;29(40):6834-7.
127. Dicko A, Odusanya OO, Diallo AI, Santara G, Barry A, Dolo A, et al. Primary vaccination with the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in infants in Mali and Nigeria: a randomized controlled trial. BMC Public Health. 2011;11:882.
128. Ruiz-Palacios GM, Guerrero ML, Hernandez-Delgado L, Lavalle-Villalobos A, Casas-Munoz A, Cervantes-Apolinar Y, et al. Immunogenicity, reactogenicity and safety of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in Mexican infants. Hum Vaccin. 2011;7(11):1137-45.
129. Van den Bergh MR, Spijkerman J, Francois N, Swinnen K, Borys D, Schuerman L, et al. Immunogenicity, safety, and reactogenicity of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine and DTPa-IPV-Hib when coadministered as a 3-dose primary vaccination schedule in The Netherlands: a randomized controlled trial. Pediatr Infect Dis J. 2011;30(9):e170-8.
130. Lalwani S, Chatterjee S, Chhatwal J, Verghese VP, Mehta S, Shafi F, et al. Immunogenicity, safety, and reactogenicity of the 10-valent pneumococcal non-typeable Hemophilus influenzae protein D conjugate vaccine (PHiD-CV) when co-administered with the DTPw-HBV/Hib vaccine in Indian infants: a single-blind, randomized, controlled study. Hum Vaccin Immunother. 2012;8(5):612-22.
131. Huang LM, Lin TY, Juergens C. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine given with routine pediatric vaccines in Taiwan. Vaccine. 2012;30(12):2054-9.
132. Martinon-Torres F, Gimenez-Sanchez F, Gurtman A, Bernaola E, Diez-Domingo J, Carmona A, et al. 13-valent pneumococcal conjugate vaccine given with meningococcal C-tetanus toxoid conjugate and other routine pediatric vaccinations: immunogenicity and safety. Pediatr Infect Dis J. 2012;31(4):392-9.
133. Vanderkooi OG, Scheifele DW, Girgenti D, Halperin SA, Patterson SD, Gruber WC, et al. Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine in healthy infants and toddlers given with routine pediatric vaccinations in Canada. Pediatr Infect Dis J. 2012;31(1):72-7.
134. Grimprel E, Laudat F, Patterson S, Baker SA, Sidhu MS, Gruber WC, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine

(PCV13) when given as a toddler dose to children immunized with PCV7 as infants. Vaccine. 2011;29(52):9675-83.
135. Frenck RW, Jr., Gurtman A, Rubino J, Smith W, van Cleeff M, Jayawardene D, et al. Randomized, controlled trial of a 13-valent pneumococcal conjugate vaccine administered concomitantly with an influenza vaccine in healthy adults. Clin Vaccine Immunol. 2012;19(8):1296-303.
136. Espinosa-Padilla SE, Murata C, Estrada-Parra S, Santos-Argumedo L, Mascarenas C, Franco-Paredes C, et al. Immunogenicity of a 23-valent pneumococcal polysaccharide vaccine among Mexican children. Arch Med Res. 2012;43(5):402-5.
137. Frenck RW, Jr., Yeh S. The development of 13-valent pneumococcal conjugate vaccine and its possible use in adults. Expert Opin Biol Ther. 2012;12(1):63-77.
138. Sanford M. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed): in older adults. Drugs. 2012;72(9):1243-55.
139. Musher DM, Manoff SB, McFetridge RD, Liss CL, Marchese RD, Raab J, et al. Antibody persistence ten years after first and second doses of 23-valent pneumococcal polysaccharide vaccine, and immunogenicity and safety of second and third doses in older adults. Hum Vaccin. 2011;7(9):919-28.
140. The 8th International Symposium on Pneumococci and Pneumococcal Diseases; Brazil 2012.
141. Earnshaw SR, McDade CL, Zanotti G, Farkouh RA, Strutton D. Cost-effectiveness of 2 + 1 dosing of 13-valent and 10-valent pneumococcal conjugate vaccines in Canada. BMC Infect Dis. 2012;12(1):101.
142. Kuhlmann A, Theidel U, Pletz MW, Graf von der Schulenburg JM. Potential cost-effectiveness and benefit-cost ratios of adult pneumococcal vaccination in Germany. Health Econ Rev. 2012;2(1):4.
143. Chaturvedi AK. Beyond cervical cancer: burden of other HPV-related cancers among men and women. J Adolesc Health. 2010;46(4 Suppl):S20-6.
144. Trienekens SCM, Koedijk FDH, Broek vdIVF, Vriend HJ, Op de Coul ELM, Veen vMG, et al. Sexually transmitted infections, including HIV, in the Netherlands in 2011. RIVM Report 201051001.
145. Lareb NBC. Rapportage gemelde bijwerkingen na vaccinarties in het Rijksvaccinatieprogramma 2011. 's-Hertogenbosch: Lareb; 2012.
146. Khatun S, Akram Hussain SM, Chowdhury S, Ferdous J, Hossain F, Begum SR, et al. Safety and immunogenicity profile of human papillomavirus-16/18 AS04 adjuvant cervical cancer vaccine: a randomized controlled trial in healthy adolescent girls of Bangladesh. Jpn J Clin Oncol. 2012;42(1):36-41.
147. Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland SM, Castellsagué X, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. The Lancet Oncology. 2012;13(1):89-99.
148. Wheeler CM, Harvey BM, Pichichero ME, Simon MW, Combs SP, Blatter MM, et al. Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted vaccine coadministered with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine and/or meningococcal conjugate vaccine to healthy girls 11 to 18 years of age: results from a randomized open trial. Pediatr Infect Dis J. 2011;30(12):e225-34.
149. Gee J, Naleway A, Shui I, Baggs J, Yin R, Li R, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine. 2011;29(46):8279-84.
150. Chao C, Klein NP, Velicer CM, Sy LS, Slezak JM, Takhar H, et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med. 2012;271(2):193-203.

151. Li R, Li Y, Radley D, Liu Y, Huang T, Sings HL, et al. Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: a randomized, double-blind, placebo-controlled trial in Chinese males and females. Vaccine. 2012;30(28):4284-91.
152. Mok CC, Ho LY, Fong LS, To CH. Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case-control study. Ann Rheum Dis. 2012. [Epub ahead of print].
153. Einstein MH, Baron M, Levin MJ, Chatterjee A, Fox B, Scholar S, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 vaccine and HPV-6/11/16/18 vaccine: follow-up from months 12-24 in a Phase III randomized study of healthy women aged 18-45 years. Hum Vaccin. 2011;7(12):1343-58.
154. Palefsky JM, Giuliano AR, Goldstone S, Moreira ED, Jr., Aranda C, Jessen H, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med. 2011;365(17):1576-85.
155. Vriend HJ, Boot HJ, van der Sande MaB. Type-Specific Human Papillomavirus Infections Among Young Heterosexual Male and Female STI Clinic Attendees. Sexually Transmitted Diseases. 2012;39(1):72-8.
156. Scherpenisse M, Mollers M, Schepp RM, Boot HJ, de Melker HE, Meijer CJ, et al. Seroprevalence of seven high-risk HPV types in The Netherlands. Vaccine. 2012;30(47):6686-93.
157. Scherpenisse M, Mollers M, Schepp R, Meijer C, de Melker H, Berbers G, et al. Detection of systemic and mucosal HPV-specific IgG and IgA antibodies in adolescent girls one and two years after HPV vaccination. Hum Vaccin Immunother. 2012;9(2). [Epub ahead of print].
158. Integrated Primary Care Information. Available from: http://www.ipci.nl/.
159. Bogaards JA, Coupe VM, Xiridou M, Meijer CJ, Wallinga J, Berkhof J. Long-term impact of human papillomavirus vaccination on infection rates, cervical abnormalities, and cancer incidence. Epidemiology. 2011;22(4):505-15.
160. Bogaards JA, Xiridou M, Coupe VM, Meijer CJ, Wallinga J, Berkhof J. Model-based estimation of viral transmissibility and infection-induced resistance from the age-dependent prevalence of infection for 14 high-risk types of human papillomavirus. Am J Epidemiol. 2010;171(7):817-25.
161. Bogaards JA, Kretzschmar M, Xiridou M, Meijer CJ, Berkhof J, Wallinga J. Sex-specific immunization for sexually transmitted infections such as human papillomavirus: insights from mathematical models. PLoS Med. 2011;8(12):e1001147.
162. Bogaards JA, Coupe VM, Meijer CJ, Berkhof J. The clinical benefit and cost-effectiveness of human papillomavirus vaccination for adult women in the Netherlands. Vaccine. 2011;29(48):8929-36.
163. Soergel P, Makowski L, Schippert C, Staboulidou I, Hille U, Hillemanns P. The cost efficiency of HPV vaccines is significantly underestimated due to omission of conisation-associated prematurity with neonatal mortality and morbidity. Hum Vaccin Immunother. 2012;8(2):243-51.
164. ECDC. European Centre for Disease Prevention and Control. Introduction of HPV vaccines in EU
countries – an update. Stockholm: ECDC; 2012.
165. Dutch Health Council. Screening op baarmoederhalskanker. Den Haag: Dutch Health Council;2011 Contract No.: 2011/07. ISBN 978-90-5549-841-3.
166. van Rosmalen J, de Kok IM, van Ballegooijen M. Cost-effectiveness of cervical cancer screening: cytology versus human papillomavirus DNA testing. BJOG. 2012;119(6):699-709.

167. Borgogna C, Zavattaro E, De Andrea M, Griffin HM, Dell'Oste V, Azzimonti B, et al. Characterization of beta papillomavirus E4 expression in tumours from Epidermodysplasia Verruciformis patients and in experimental models. Virology. 2012;423(2):195-204.
168. Prevention CfDCa. Withdrawal of rotavirus vaccine recommendation. MMWR Morb Mortal Wkly Rep. 1999;48:1007.
169. Geier DA, King PG, Sykes LK, Geier MR. The temporal relationship between RotaTeq immunization and intussusception adverse events in the Vaccine Adverse Event Reporting System (VAERS). Med Sci Monit. 2012;18(2):PH12-7.
170. Buttery JP, Danchin MH, Lee KJ, Carlin JB, McIntyre PB, Elliott EJ, et al. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. Vaccine. 2011;29(16):3061-6.
171. Patel MM, Lopez-Collada VR, Bulhoes MM, De Oliveira LH, Bautista Marquez A, Flannery B, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. N Engl J Med. 2011;364(24):2283-92.
172. Loughlin J, Mast TC, Doherty MC, Wang FT, Wong J, Seeger JD. Postmarketing evaluation of the short-term safety of the pentavalent rotavirus vaccine. Pediatr Infect Dis J. 2012;31(3):292-6.
173. Shui IM, Baggs J, Patel M, Parashar UD, Rett M, Belongia EA, et al. Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. JAMA. 2012;307(6):598-604.
174. Justice F, Carlin J, Bines J. Changing epidemiology of intussusception in Australia. J Paediatr Child Health. 2005;41(9-10):475-8.
175. Bines JE, Patel M, Parashar U. Assessment of postlicensure safety of rotavirus vaccines, with emphasis on intussusception. J Infect Dis. 2009;200 Suppl 1:S282-90.
176. Noguchi A, Nakagomi T, Kimura S, Takahashi Y, Matsuno K, Koizumi H, et al. Incidence of Intussusception as Studied from a Hospital-Based Retrospective Survey over a 10-Year Period (2001-2010) in Akita Prefecture, Japan. Jpn J Infect Dis. 2012;65(4):301-5.
177. Dang DA, Nguyen VT, Vu DT, Nguyen TH, Nguyen DM, Yuhuan W, et al. A dose-escalation safety and immunogenicity study of a new live attenuated human rotavirus vaccine (Rotavin-M1) in Vietnamese children. Vaccine. 2012;30 Suppl 1:A114-21.
178. Sow SO, Tapia M, Haidara FC, Ciarlet M, Diallo F, Kodio M, et al. Efficacy of the oral pentavalent rotavirus vaccine in Mali. Vaccine. 2012;30 Suppl 1:A71-8.
179. Banda R, Yambayamba V, Lalusha BD, Sinkala E, Kapulu MC, Kelly P. Safety of live, attenuated oral vaccines in HIV-infected Zambian adults: Oral vaccines in HIV. Vaccine. 2012;30(38):5656-60.
180. Kim JS, Bae CW, Lee KY, Park MS, Choi YY, Kim KN, et al. Immunogenicity, reactogenicity and safety of a human rotavirus vaccine (RIX4414) in Korean infants: A randomized, double-blind, placebo-controlled, phase IV study. Hum Vaccin Immunother. 2012;8(6):806-12.
181. Omenaca F, Sarlangue J, Szenborn L, Nogueira M, Suryakiran PV, Smolenov IV, et al. Safety, reactogenicity and immunogenicity of the human rotavirus vaccine in preterm European infants: a randomized phase IIIb study. Pediatr Infect Dis J. 2012;31(5):487-93.
182. Laserson KF, Nyakundi D, Feikin DR, Nyambane G, Cook E, Oyieko J, et al. Safety of the pentavalent rotavirus vaccine (PRV), RotaTeq((R)), in Kenya, including among HIV-infected and HIV-exposed infants. Vaccine. 2012;30 Suppl 1:A61-70.

183. Bruijning-Verhagen P, Sankatsing V, Kunst A, van den Born C, Bleeker E, Thijsen S, et al. Rotavirus Related Hospitalizations are Responsible for High Seasonal Peaks in All-Cause Pediatric Hospitalizations. PIDJ. 2012;31(12):e244-9.
184. Haverkate M, D'Ancona F, Giambi C, Johansen K, Lopalco PL, Cozza V, et al. Mandatory and recommended vaccination in the EU, Iceland and Norway: Results of the VENICE 2010 survey on the ways of implementing national vaccination programmes. Eurosurveillance. 2012;17(22).
185. Phua KB, Lim FS, Lau YL, Nelson EA, Huang LM, Quak SH, et al. Rotavirus vaccine RIX4414 efficacy sustained during the third year of life: a randomized clinical trial in an Asian population. Vaccine. 2012;30(30):4552-7.
186. Desai R, Curns AT, Steiner CA, Tate JE, Patel MM, Parashar UD. All Cause Gastroenteritis and Rotavirus-Coded Hospitalizations among US Children from 2000-2009. Clin Infect Dis. 2012;55(4):e28-34.
187. Braeckman T, Van Herck K, Meyer N, Pircon JY, Soriano-Gabarro M, Heylen E, et al. Effectiveness of rotavirus vaccination in prevention of hospital admissions for rotavirus gastroenteritis among young children in Belgium: case-control study. BMJ. 2012;345:e4752.
188. Martinon-Torres F, Martinon-Torres N, Alejandro MB, Collazo LR, Pertega-Diaz S, Seoane-Pillado MT, et al. Acute gastroenteritis hospitalizations among children aged < 5 years before and after introduction of rotavirus vaccines: A hospital-based surveillance study in Galicia, Spain. Hum Vaccin Immunother. 2012;8(7):946-52.
189. Laszlo B, Konya J, Dandar E, Deak J, Farkas A, Gray J, et al. Surveillance of human rotaviruses in 2007-2011, Hungary: exploring the genetic relatedness between vaccine and field strains. J Clin Virol. 2012;55(2):140-6.
190. Dulgheroff AC, Figueiredo EF, Moreira LP, Moreira KC, Moura LM, Gouvea VS, et al. Distribution of rotavirus genotypes after vaccine introduction in the Triangulo Mineiro region of Brazil: 4-Year follow-up study. J Clin Virol. 2012;55(1):67-71.
191. Wendy B. Vaccination with 3-dose paediatric rotavirus vaccine (RotaTeq®): Impact on the timeliness of uptake of the primary course of DTPa vaccine. Vaccine. 2012;30(35):5293-7.
192. Postma MJ, Jit M, Rozenbaum MH, Standaert B, Tu HA, Hutubessy RC. Comparative review of three cost-effectiveness models for rotavirus vaccines in national immunization programs; a generic approach applied to various regions in the world. BMC Med. 2011;9:84.
193. Donker GA. Continuous Morbidity Registration Sentinel Stations the Netherlands 2010. Utrecht: Nivel; 2011.
194. Stirbu-Wagner I, Visscher S, Davids R, Gravestein JV, Ursum J, Van Althuis T, et al. National Information Network Primary Care (LINH): Facts and figures on primary care in the Netherlands. Utrecht/Nijmegen: NIVEL/IQ; 2011.
195. Bartelds AIM. Continuous Morbidity Registration Sentinel Stations the Netherlands 2001. Utrecht: Nivel; 2002.
196. Plotkin SA, Orenstein WA, Offit PA. Vaccines. Philadelphia: Elsevier; 2008.
197. Deckers JGM, Schellevis FG. Health information from primary care: final report December 1, 2001 - March 31, 2004. Utrecht: Netherlands Institute for Health Services Research (NIVEL); 2004.
198. Dutch Hospital Data. National Medical Register. Utrecht: Dutch Hospital Data; 2008-2011.
199. Statistics Netherlands. Deaths by main primary cause of death, sex and age; 2000-2011. Voorburg: CBS.

200. Mahamud A, Marin M, Nickell SP, Shoemaker T, Zhang JX, Bialek SR. Herpes zoster-related deaths in the United States: validity of death certificates and mortality rates, 1979-2007. Clin Infect Dis. 2012;55(7):960-6.
201. De Melker H, Berbers G, Hahne S, Rumke H, van den Hof S, de Wit A, et al. The epidemiology of varicella and herpes zoster in the Netherlands: implications for varicella zoster virus vaccination. Vaccine. 2006;24(18):3946-52.
202. Van Lier A, Smits G, Mollema L, Waaijenborg S, Berbers G, van der Klis F, et al. Varicella zoster virus infection occurs at young age in the Netherlands. 30th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID), Thessaloniki, Greece, May 8-12, 2012.
203. Waaijenborg S, Hahné S, Knol M, Mollema L, Smits G, Berbers G, et al. Identifying number of contacts as a determinant of hazard for varicella infection using current status survival analysis. 33rd Annual Conference of the International Society for Clinical Biostatistics (ISCB), Bergen, Norway, August 19-13, 2012.
204. Zell R, Taudien S, Pfaff F, Wutzler P, Platzer M, Sauerbrei A. Sequencing of 21 varicella-zoster virus genomes reveals two novel genotypes and evidence of recombination. J Virol. 2012;86(3):1608-22.
205. Schmidt-Chanasit J, Sauerbrei A. Evolution and world-wide distribution of varicella-zoster virus clades. Infect Genet Evol. 2011;11(1):1-10.
206. Sauerbrei A, Stefanski J, Philipps A, Krumbholz A, Zell R, Wutzler P. Monitoring prevalence of varicella-zoster virus clades in Germany. Med Microbiol Immunol. 2011;200(2):99-107.
207. O'Leary ST, Suh CA, Marin M. Febrile seizures and measles-mumps-rubella-varicella (MMRV) vaccine: What do primary care physicians think? Vaccine. 2012;30(48):6731-3.
208. Blatter MM, Klein NP, Shepard JS, Leonardi M, Shapiro S, Schear M, et al. Immunogenicity and Safety of Two Tetravalent (Measles, Mumps, Rubella, Varicella) Vaccines Coadministered With Hepatitis A and Pneumococcal Conjugate Vaccines to Children Twelve to Fourteen Months of Age. Pediatr Infect Dis J. 2012;31(8):e133-e40.
209. Barbosa CM, Terreri MT, Rosario PO, de Moraes-Pinto MI, Silva CA, Hilario MO. Immune response and tolerability of varicella vaccine in children and adolescents with systemic lupus erythematosus previously exposed to varicella-zoster virus. Clin Exp Rheumatol. 2012;30(5):791-8.
210. Chou JF, Kernan NA, Prockop S, Heller G, Scaradavou A, Kobos R, et al. Safety and immunogenicity of the live attenuated varicella vaccine following T replete or T cell-depleted related and unrelated allogeneic hematopoietic cell transplantation (alloHCT). Biol Blood Marrow Transplant. 2011;17(11):1708-13.
211. Fridman D, Monti A, Bonnet MC, Armoni J, Stamboulian D. Safety of a second dose of varicella vaccine administered at 4 to 6 years of age in healthy children in Argentina. Hum Vaccin. 2011;7(10):1066-71.
212. Ruger G, Gabutti G, Rumke H, Rombo L, Bernaola E, Diez-Domingo J, et al. Safety of a Two-Dose Regimen of a Combined Measles, Mumps, Rubella and Varicella Live Vaccine Manufactured with Recombinant Human Albumin. Pediatr Infect Dis J. 2012;31(11):1166-72.
213. Vesikari T, Becker T, Gajdos V, Fiquet A, Thomas S, Richard P, et al. Immunogenicity and safety of a two-dose regimen of a combined measles, mumps, rubella and varicella live vaccine (ProQuad((R))) in infants from 9 months of age. Vaccine. 2012;30(20):3082-9.
214. European Medicines Agency (EMA). Zostavax; Procedural steps taken and scientific information after the authorisation. London: EMA; 2012.

215. Schmader KE, Levin MJ, Gnann JW, Jr., McNeil SA, Vesikari T, Betts RF, et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. Clin Infect Dis. 2012;54(7):922-8.
216. Murray AV, Reisinger KS, Kerzner B, Stek JE, Sausser TA, Xu J, et al. Safety and tolerability of zoster vaccine in adults >/=60 years old. Hum Vaccin. 2011;7(11):1130-6.
217. Vermeulen JN, Lange JM, Tyring SK, Peters PH, Nunez M, Poland G, et al. Safety, tolerability, and immunogenicity after 1 and 2 doses of zoster vaccine in healthy adults >/=60 years of age. Vaccine. 2012;30(5):904-10.
218. Tseng HF, Liu A, Sy L, Marcy SM, Fireman B, Weintraub E, et al. Safety of zoster vaccine in adults from a large managed-care cohort: a Vaccine Safety Datalink study. J Intern Med. 2012;271(5):510-20.
219. Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA. 2012;308(1):43-9.
220. Leroux-Roels I, Leroux-Roels G, Clement F, Vandepapeliere P, Vassilev V, Ledent E, et al. A Phase 1/2 Clinical Trial Evaluating Safety and Immunogenicity of a Varicella Zoster Glycoprotein E Subunit Vaccine Candidate in Young and Older Adults. J Infect Dis. 2012;206(8):1280-90.
221. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med. 1999;38(4-5):339-44.
222. Lamberts H, Wood M, Hofmans-Okkes IM. International primary care classifications: the effect of fifteen years of evolution. Fam Pract. 1992;9(3):330-9.
223. Van der Lei J, Duisterhout JS, Westerhof HP, van der Does E, Cromme PV, Boon WM, et al. The introduction of computer-based patient records in the Netherlands. Ann Intern Med. 1993;119(10):1036-41.
224. Pierik JG, Gumbs PD, Fortanier SA, Van Steenwijk PC, Postma MJ. Epidemiological characteristics and societal burden of varicella zoster virus in the Netherlands. BMC Infect Dis. 2012;12:110.
225. Statistics Netherlands. Population: age, country of origin, sex and region (1 January). Voorburg: CBS; 2012.
226. Bilcke J, Ogunjimi B, Marais C, F DES, Callens M, Callaert K, et al. The health and economic burden of chickenpox and herpes zoster in Belgium. Epidemiol Infect. 2012;140(11):2096-109.
227. Wolleswinkel-van den Bosch JH, Speets AM, Rumke HC, Gumbs PD, Fortanier SC. The burden of varicella from a parent's perspective and its societal impact in The Netherlands: an Internet survey. BMC Infect Dis. 2011;11:320.
228. Van Lier A, van der Maas NA, Rodenburg GD, Sanders EA, de Melker HE. Hospitalization due to varicella in the Netherlands. BMC Infect Dis. 2011;11:85.
229. Szucs TD, Kressig RW, Papageorgiou M, Kempf W, Michel JP, Fendl A, et al. Economic evaluation of a vaccine for the prevention of herpes zoster and post-herpetic neuralgia in older adults in Switzerland. Hum Vaccin. 2011;7(7):749-56.
230. Bilcke J, Marais C, Ogunjimi B, Willem L, Hens N, Beutels P. Cost-effectiveness of vaccination against herpes zoster in adults aged over 60 years in Belgium. Vaccine. 2012;30(3):675-84.
231. Bilcke J, Ogunjimi B, Hulstaert F, Van Damme P, Hens N, Beutels P. Estimating the age-specific duration of herpes zoster vaccine protection: a matter of model choice? Vaccine. 2012;30(17):2795-800.
232. Schmader K, Oxman M, Levin M, Johnson G, Zhang J, Betts R, et al. Persistence of the Efficacy of Zoster Vaccine in the Shingles Prevention Study and the Short-Term Persistence Substudy. Clin Infect Dis. 2012;55(10):1320-8.

233. Van Hoek AJ, Melegaro A, Gay N, Bilcke J, Edmunds WJ. The cost-effectiveness of varicella and combined varicella and herpes zoster vaccination programmes in the United Kingdom. Vaccine. 2012;30(6):1225-34.
234. Goldman GS, King PG. Review of the United States universal varicella vaccination program: Herpes zoster incidence rates, cost-effectiveness, and vaccine efficacy based primarily on the Antelope Valley Varicella Active Surveillance Project data. Vaccine. 2012. [Epub ahead of print].
235. Fournet N, Baas D, van Pelt W, Swaan C, Ober H, Isken L, et al. Another possible food-borne outbreak of hepatitis A in the Netherlands indicated by two closely related molecular sequences, July to October 2011. Euro Surveill. 2012;17(6):18-20.
236. Irving GJ, Holden J, Yang R, Pope D. Hepatitis A immunisation in persons not previously exposed to hepatitis A. Cochrane Database Syst Rev. 2012;7:CD009051.
237. Rinderknecht S, Michaels MG, Blatter M, Gaglani M, Andrews W, Abughali N, et al. Immunogenicity and safety of an inactivated hepatitis A vaccine when coadministered with measles-mumps-rubella and varicella vaccines in children less than 2 years of age. Pediatr Infect Dis J. 2011;30(10):e179-85.
238. Zhang ZL, Zhu XJ, Wang X, Liang M, Sun J, Liu Y, et al. Interchangeability and tolerability of two inactivated hepatitis A vaccines in Chinese children. Vaccine. 2012;30(27):4028-33.
239. Zheng H, Chen Y, Wang F, Gong X, Wu Z, Miao N, et al. Comparing live attenuated and inactivated hepatitis A vaccines: an immunogenicity study after one single dose. Vaccine. 2011;29(48):9098-103.
240. Suijkerbuijk AW, Lugner AK, van Pelt W, Wallinga J, Verhoef LP, de Melker HE, et al. Assessing potential introduction of universal or targeted hepatitis A vaccination in the Netherlands. Vaccine. 2012;30(35):5199-205.
241. Verhoef L, Boot HJ, Koopmans M, Mollema L, Van Der Klis F, Reimerink J, et al. Changing risk profile of hepatitis A in The Netherlands: a comparison of seroprevalence in 1995-1996 and 2006-2007. Epidemiol Infect. 2011;139(8):1172-80.
242. Ott JJ, Irving G, Wiersma ST. Long-term protective effects of hepatitis A vaccines. A systematic review. Vaccine. 2012;31(1):3-11.
243. Van Herck K, Crasta PD, Messier M, Hardt K, Van Damme P. Seventeen-year antibody persistence in adults primed with two doses of an inactivated hepatitis A vaccine. Hum Vaccin Immunother. 2012;8(3):323-7.
244. Hendrickx G, Vorsters A, Van Damme P. Advances in hepatitis immunization (A, B, E): public health policy and novel vaccine delivery. Curr Opin Infect Dis. 2012;25(5):578-83.
245. Sharapov UM, Bulkow LR, Negus SE, Spradling PR, Homan C, Drobeniuc J, et al. Persistence of hepatitis A vaccine induced seropositivity in infants and young children by maternal antibody status: 10-year follow-up. Hepatology. 2012;56(2):516-22.
246. Marshall HS, Richmond PC, Nissen MD, Jiang Q, Anderson AS, Jansen KU, et al. Safety and Immunogenicity of a Meningococcal B Bivalent rLP2086 Vaccine in Healthy Toddlers Aged 18-36 Months: A Phase 1 Randomized-controlled Clinical Trial. Pediatr Infect Dis J. 2012;31(10):1061-8.
247. Santolaya ME, O'Ryan ML, Valenzuela MT, Prado V, Vergara R, Munoz A, et al. Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observer-blind, placebo-controlled study. Lancet. 2012;379(9816):617-24.
248. Van de Waterbeemd B, Streefland M, van Keulen L, van den Ijssel J, de Haan A, Eppink MH, et al. Identification and optimization of critical process

parameters for the production of NOMV vaccine against Neisseria meningitidis. Vaccine. 2012;30(24):3683-90.
249. Kaaijk P, van Straaten I, van de Waterbeemd B, Boot EPJ, Level LMAR, van Dijken HH, et al. Preclinical safety and immunogenicity evaluation of a nonavalent PorA native outer membrane vesicle vaccine against serogroup B meningococcal disease. Vaccine. 2013;31(7):1065-71.
250. Kaaijk P, van der Ark AA, van Amerongen G, van den Dobbelsteen GP. Nonclinical vaccine safety evaluation: advantages of continuous temperature monitoring using abdominally implanted data loggers. J Appl Toxicol. 2012. [Epub ahead of print].
251. Serruto D, Bottomley MJ, Ram S, Giuliani MM, Rappuoli R. The new multicomponent vaccine against meningococcal serogroup B, 4CMenB: immunological, functional and structural characterization of the antigens. Vaccine. 2012;30 Suppl 2:B87-97.
252. Richmond PC, Marshall HS, Nissen MD, Jiang Q, Jansen KU, Garces-Sanchez M, et al. Safety, immunogenicity, and tolerability of meningococcal serogroup B bivalent recombinant lipoprotein 2086 vaccine in healthy adolescents: a randomised, single-blind, placebo-controlled, phase 2 trial. Lancet Infect Dis. 2012;12(8):597-607.
253. Pinto VB, Moran EE, Cruz F, Wang XM, Fridman A, Zollinger WD, et al. An experimental outer membrane vesicle vaccine from N. meningitidis serogroup B strains that induces serum bactericidal activity to multiple serogroups. Vaccine. 2011;29(44):7752-8.
254. Broker M, Jacobsson S, Detora L, Pace D, Taha MK. Increase of meningococcal serogroup Y cases in Europe: A reason for concern? Hum Vaccin Immunother. 2012;8(5):685-8.
255. U.S. Department of Health and Human Services. The Jordan Report; Accelerated development of vaccines 2012. Washington D.C.: U.S. Department of Health and Human Services 2012.
256. Meijboom MJ, Rozenbaum MH, Benedictus A, Luytjes W, Kneyber MC, Wilschut JC, et al. Cost-effectiveness of potential infant vaccination against respiratory syncytial virus infection in The Netherlands. Vaccine. 2012;30(31):4691-700.
257. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med. 2005;352(17):1749-59.
258. KNCV Tuberculosefonds. Available from: www.tbc-online.nl.
259. Stichting HIV Monitoring. Available from: http://www.hiv-monitoring.nl/index.php/nederlands/.
260. WHO. Hepatitis C fact sheet. Available from: http://www.who.int/mediacentre/factsheets/fs164/en/index.html.
261. Hensgens M.P.M. Sixth Annual Report of the National Reference Laboratory for Clostridium difficile (May 2011 to May 2012) and results of the sentinel surveillance. 02-07-2012.
262. Hoogkamp-Korstanje JA, Gerards LJ, Cats BP. Maternal carriage and neonatal acquisition of group B streptococci. J Infect Dis. 1982;145(6):800-3.
263. Dempsey AF, Pangborn HM, Prosser LA. Cost-effectiveness of routine vaccination of adolescent females against cytomegalovirus. Vaccine. 2012;30(27):4060-6.
264. Op de Coul EL, van Weert JW, Oomen PJ, Smit C, van der Ploeg CP, Hahne SJ, et al. [Antenatal screening in the Netherlands for HIV, hepatitis B and syphilis is effective]. Ned Tijdschr Geneeskd. 2010;154:A2175.

List of abbreviations

ACIP	Advisory Committee on Immunisation Practices
ACS	Amsterdam Cohort Study
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
Bbio	Bilthoven Biologicals
BCG	Bacille Calmette Guérin
betaPV	Beta papillomavirus
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
CRS	Congenital Rubella Syndrome
CSF	cerebrospinal fluid
CVP	childhood vaccine providers
CVS	cervical secretion samples
CWC	child welfare centres
DNA	desoxyribonucleïnezuur
DTP	combination of diphtheria, tetanus, and pertussis vaccines
ECDC	European Centre for Disease Control and Prevention
EMA	European Medicines Agency
EMRs	electronic medical records
EPI	Department of Epidemiology and Surveillance
EU	European Union
EV	Enterovirus
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
HAVANA	Study of the HPV prevalence among young girls
HBsAg	hepatitis B surface antigen

HBV	hepatitis B virus
HCV	hepatitis C virus
HGAIN	high-grade anal intraepithelial neoplasia
Hib	*Haemophilus influenzae* type b
HibMenC-TT	*Haemophilus influenzae* type b and *Neisseria meningitidis* serogroup C tetanus toxoid conjugate vaccine
HIV	human immunodeficiency virus
HPV	human papillomavirus
hrHPV	high-risk Human papillomavirus
HAS	human serum albumin
HVI	HIV Vaccine Initiative
ICD	International Classification of Diseases
ICER	Incremental cost effectiveness ratio
ICPC	International Classification of Primary Care
ICU	Intensive care unit
IDU	injecting drug user
Ig	Immunoglobulin
IL	interleukin
IPCI	Integrated Primary Care Information
IBD	invasivasive bacterial disease
IMD	invasive meningococcal disease
IPD	invasive pneumococcal disease
IPV	inactivated polio vaccine
IR	incidence rates
IU	international units
i-VDPV	VDPVs that can be attributed to an immuno-compromised person
JIA	juvenile idiopathic arthritis
LCI	National Coordination of Infectious Disease Control
LINH	the Netherlands Information Network of General Practice
LIS	Laboratory of Infectious Diseases and Perinatal Screening
LMR	National Medical Registration
LPS	lipopolysacharide
lrHPV	low-risk Human papillomavirus
LUMC	Leiden University Medical Center
LVC	low vaccination coverage
MenACWY-CRM	quadrivalent meningococcal CMR conjugate vaccine
MenACWY-D	quadrivalent meningococcal diphtheria toxoid conjugate vaccine
MenACWY-TT	tetravalent meningococcal tetanus toxoid conjugate vaccine
MenA	Meningococcal serogroup A
MenB	Meningococcal serogroup B
MenC	Meningococcal serogroup C
MenW	Meningococcal serogroup W
MenY	Meningococcal serogroup Y
MHS	Municipal Health Service (GGD)
MMR	combination of measles, mumps, and rubella vaccines
MM6	human monocytic cell line

MMRV	combination of measles, mumps, rubella, and Varicella vaccines
mOPV	monovalent oral polio vaccine
MPL	monophosphoryl lipid A
MRSA	Methicilline-resistant *Staphylococcus aureus*
MSCRAMM	microbial surface components recognising adhesive matrix molecules
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
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
NS	nation wide sample
NT	neutralisation test
NTR	Nederlandse Tuberculose Register
NVI	Netherlands Vaccine Institute
OMT	outbreak management team
OMV	outer membrane vesicle
OPV	oral polio vaccine
PALGA	the nationwide network and registry of histo- and cytopathology in the Netherlands
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PIEN	study on cellular and humoral immune response induced by the 10- and 13-valent pneumococcal vaccine
PIENTER	assessing immunisation effect to evaluate the NIP
PIM	pneumococcal vaccination trial
PLY	Pneumolysin
Prn	Pertactin
QALY	quality-adjusted life year
QC	quality control
RCT	Randomised Controlled Trial
rHA	recombinant human albumin
RIVM	National Institute for Public Health and the Environment, the Netherlands
RR	Relative risk
RSV	respiratory syncytial virus
RV	Rotavirus
SAE	serious adverse event
SBA	serum bacterial activity
SCC	Squamous cell carcinoma
SHM	national database of the HIV treatment centres
SLE	Systemische lupus erythematodes
SPC	Summary of Product Characteristics
STI	sexually transmitted infections

TB	tuberculosis
TCI	Transcutaneous immunisation
Tdap	tetanus, diphtheria and pertussis vaccine
TIG	tetanus immune globulin
TIM	Tweede Immunisatie Meningokokken C
TQS	Tetanus quick stick
UNAIDS	United Nations Programme on HIV/AIDS
VAD	Vaccine antigen deficient
VAERS	Vaccine Adverse Event Reporting System
VAPP	vaccine-associated paralytic polio
VDPV	Vaccine-derived polio virus
VE	vaccine effectiveness
VLP	Virus-Like Particle
VPD	vaccine preventable disease
VZV	varicella zoster virus
VWS	Ministry of Health, Welfare and Sport
WHO	World Health Organisation
wP	whole-cell pertussis
WPV	wild poliomyelitis virus
WRAIR	Walter Reed Army Institute of Research
ZGA	Zorggroep Almere
4CMenB	multicomponent meningococcal B vaccine

Appendix 1 Vaccine coverage for infants targeted for HBV vaccination in the NIP, birth cohorts 2003-2011

Birth cohort	Indication	Vaccination	Number eligible	Number vaccinated	Coverage
2011	D (mother is HBsAg+)	Hep B-0	546	542	99.3% [a]
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%
2009	D (mother is HBsAg+)	Hep B completed	540	519	96.1%
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%
2009	E (parent(s) migrant)	Hep B completed	37,724	35,582	94.3%
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%
2009	DS (Down syndrome)	Hep B completed	97 [b]	93	95.9%
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 one third 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)[264].

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

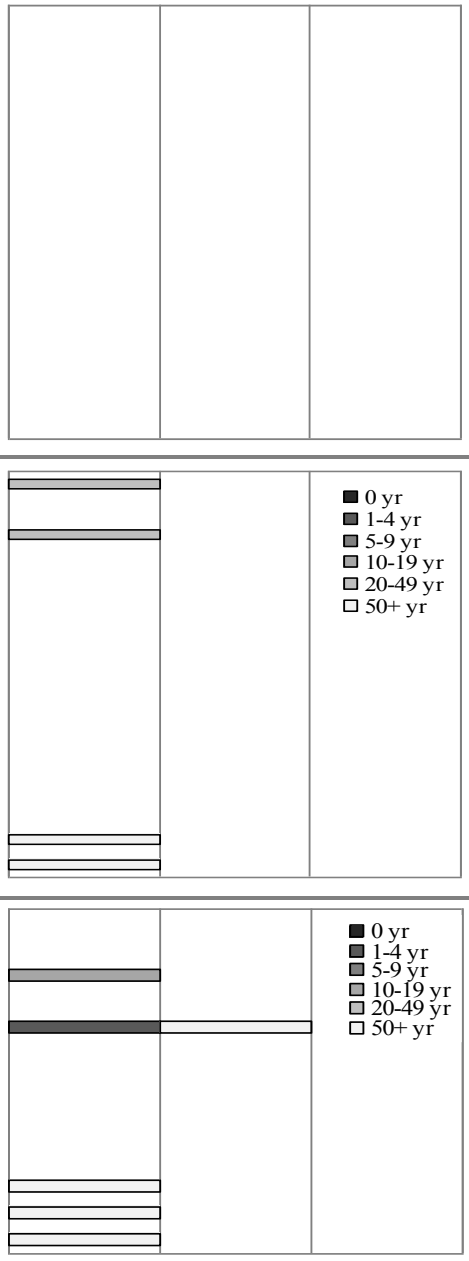
Data on notifications were retrieved from:
http://rivm.nl/Onderwerpen/Ziekten_Aandoeningen

Data on hospitalisations were retrieved from the National Medical Registration (LMR). 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	N
Mortality	1997	0	0	0	0	0	0	0	
	1998	0	0	0	0	0	0	0	
	1999	0	0	0	0	0	0	0	
	2000	0	0	0	0	0	0	0	
	2001	0	0	0	0	0	0	0	
	2002	0	0	0	0	0	0	0	
	2003	0	0	0	0	0	0	0	
	2004	0	0	0	0	0	0	0	
	2005	0	0	0	0	0	0	0	
	2006	0	0	0	0	0	0	0	
	2007	0	0	0	0	0	0	0	
	2008	0	0	0	0	0	0	0	
	2009	0	0	0	0	0	0	0	
	2010	0	0	0	0	0	0	0	
	2011	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	
	2011	0	0	0	0	0	1	1	
	2012*	0	0	0	0	0	1	1	
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	
	2011	0	0	0	0	0	1	1	

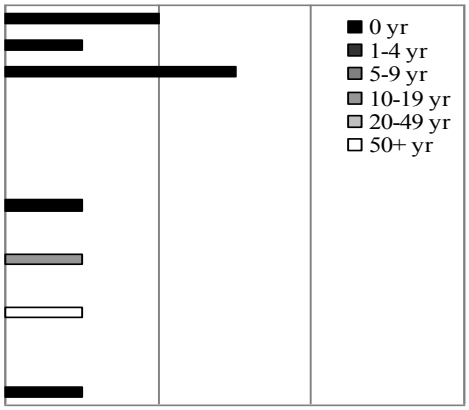


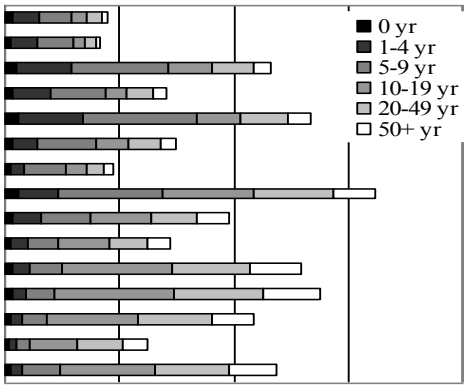
*Until Septembre 2012.

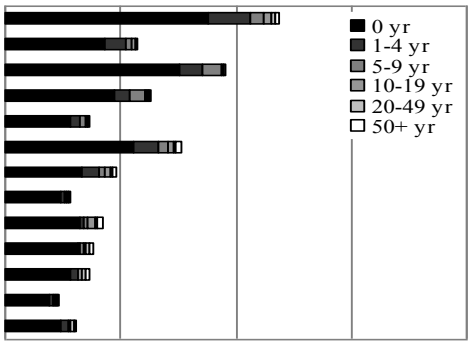
		Age (Years)							
		0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**	**Total**	N
Isolates	2000	0	0	0	0	0	0	0	
	2001	0	0	0	0	0	1	1	
	2002	0	0	0	0	0	0	0	
	2003	0	0	0	0	0	0	0	
	2004	-	-	-	-	-	-	1	
	2005	0	0	0	0	0	0	0	
	2006	0	0	0	0	0	0	0	
	2007	0	0	0	0	1	0	1	
	2008	0	0	0	0	0	0	0	
	2009	0	0	0	0	0	0	0	
	2010	0	0	0	0	0	0	0	
	2011	0	0	0	0	0	1	1	

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
	2011	1	0	0	0	0	0	1
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
	2011	159	277	1003	2491	1965	1216	7111
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
	2011	97	11	2	4	4	6	124



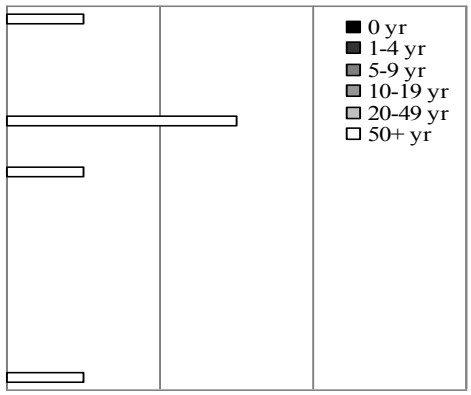


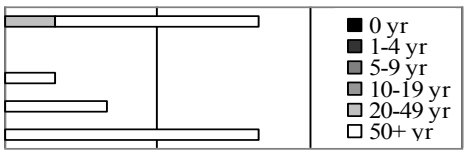


Tetanus **ICD9 037, 7713** **ID10 A33-35**

		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
	2011	0	0	0	0	0	1	1
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
	2011	0	0	0	0	0	5	5

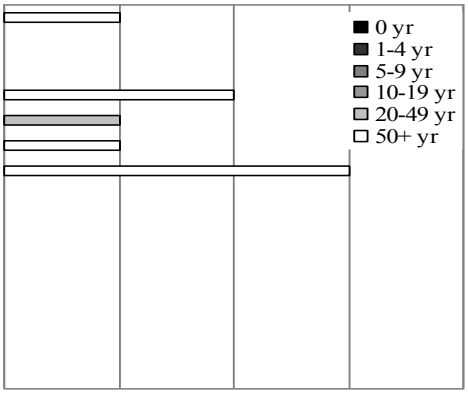
N





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

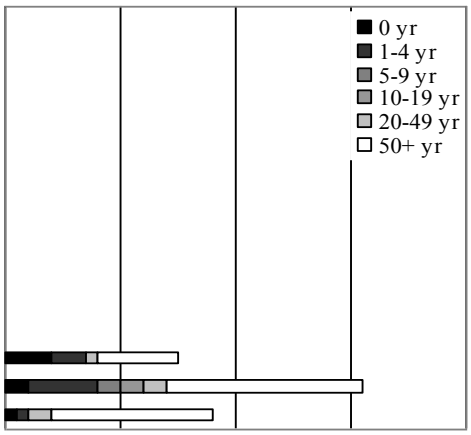
		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Mortality (Acute)	1997	0	0	0	0	0	1	1
	1998	0	0	0	0	0	0	0
	1999	0	0	0	0	0	0	0
	2000	0	0	0	0	0	2	2
	2001	0	0	0	0	1	0	1
	2002	0	0	0	0	0	1	1
	2003	0	0	0	0	0	3	3
	2004	0	0	0	0	0	0	0
	2005	0	0	0	0	0	0	0
	2006	0	0	0	0	0	0	0
	2007	0	0	0	0	0	0	0
	2008	0	0	0	0	0	0	0
	2009	0	0	0	0	0	0	0
	2010	0	0	0	0	0	0	0
	2011	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
	2011	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
	2011	0	0	0	0	0	0	0

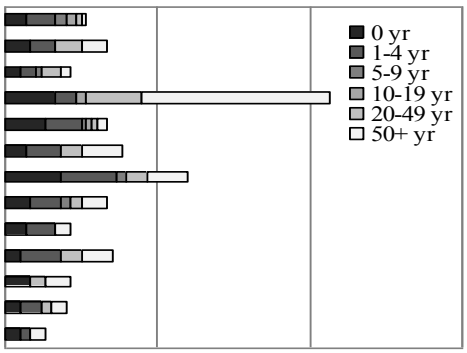


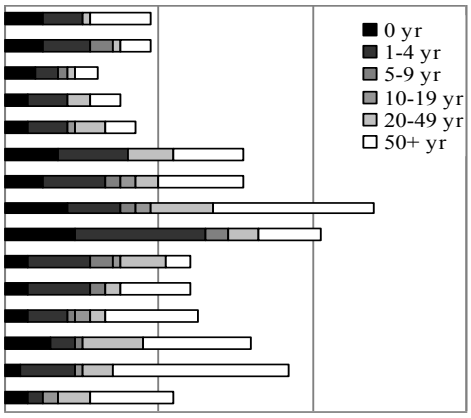
Hib **ICD9 3200** **ICD10 A41.5 G00.0**

		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	4	3	0	0	2	6	15
	2010	2	6	2	2	2	17	31
	2011	1	1	0	0	3	13	18
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
	2011	3	2	0	0	0	3	8
Isolates	1997	5	5	0	0	1	8	19
	1998	5	6	3	0	1	4	19
	1999	4	3	1	0	1	3	12
	2000	3	5	0	0	3	4	15
	2001	3	5	0	1	4	4	17
	2002	7	9	0	0	6	9	31
	2003	5	8	2	2	3	11	31
	2004	8	7	2	2	8	21	48
	2005	9	17	3	0	4	8	41
	2006	3	8	3	1	6	3	24
	2007	3	8	2	0	2	9	24
	2008	3	5	1	2	2	12	25
	2009	6	3	1	0	8	14	32
	2010	2	7	0	1	4	23	37
	2011	3	2	0	2	4	11	22

N





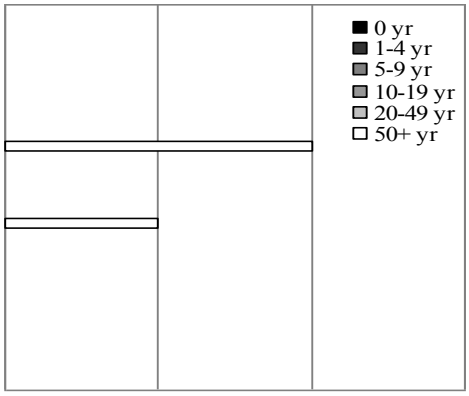


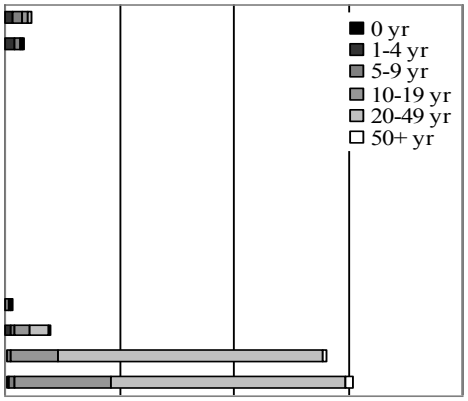
*For some patients the age is unknown.

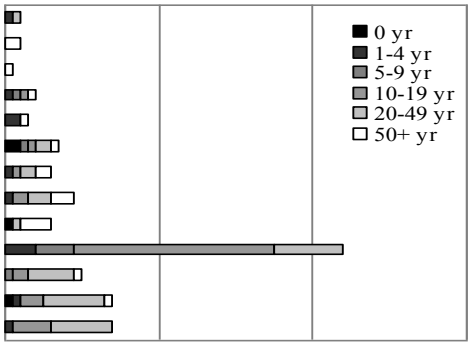
Mumps **ICD9 072** **ICD10 B26**

		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
	2011	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
	2011	2	5	9	168	410	15	609
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
	2011	0	1	0	5	8	1	14

N



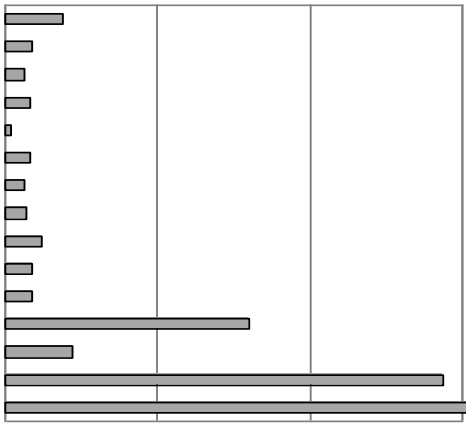




* No notifications between April 1st 1999 – December 31st 2008.

	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	
2011	-	-	-	-	-	-	190	

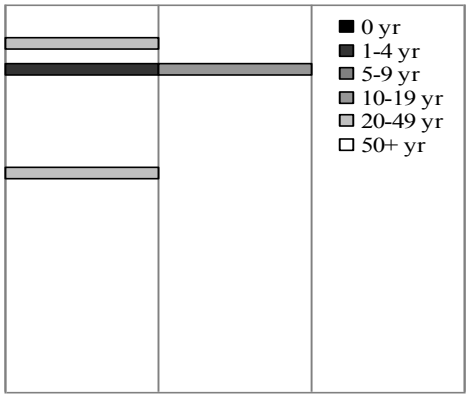
Isolates

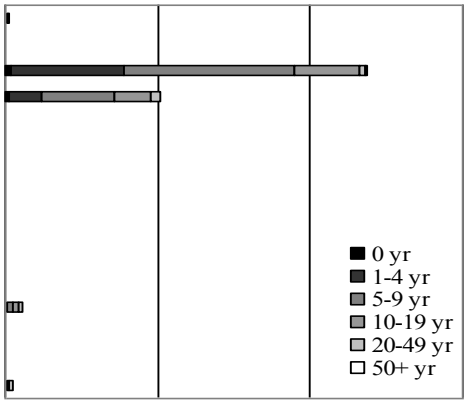


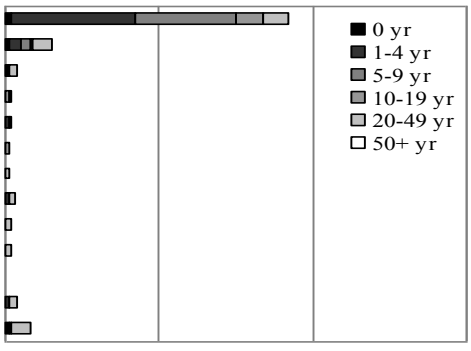
Measles **ICD9 055** **ICD10 B05**

		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
	2011	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
	2011	2	2	6	14	26	0	50
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
	2011	1	0	0	1	6	0	9

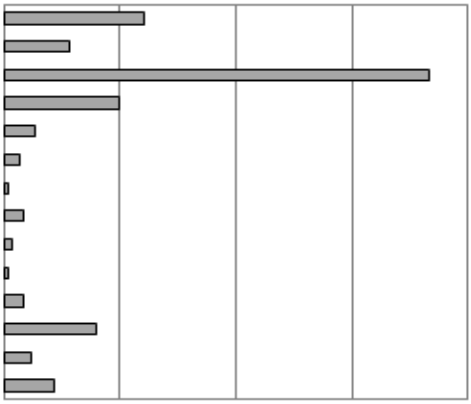
N







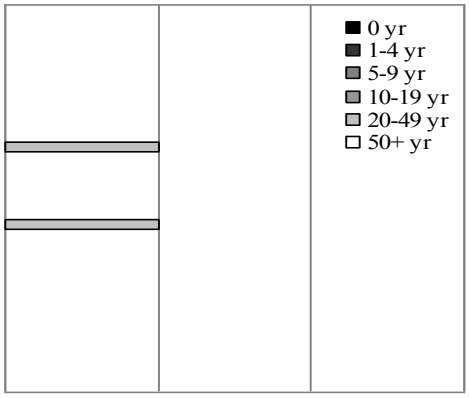
		Age (Years)							
		0	1-4	5-9	10-19	20-49	50+	Total	N
Isolates	1997	-	-	-	-	-	-	36	
	1998	-	-	-	-	-	-	17	
	1999	-	-	-	-	-	-	110	
	2000	-	-	-	-	-	-	30	
	2001	-	-	-	-	-	-	8	
	2002	-	-	-	-	-	-	4	
	2003	-	-	-	-	-	-	1	
	2004	-	-	-	-	-	-	5	
	2005	-	-	-	-	-	-	2	
	2006	-	-	-	-	-	-	1	
	2007	-	-	-	-	-	-	5	
	2008	-	-	-	-	-	-	24	
	2009	-	-	-	-	-	-	7	
	2010	-	-	-	-	-	-	13	
	2011	-	-	-	-	-	-	8	

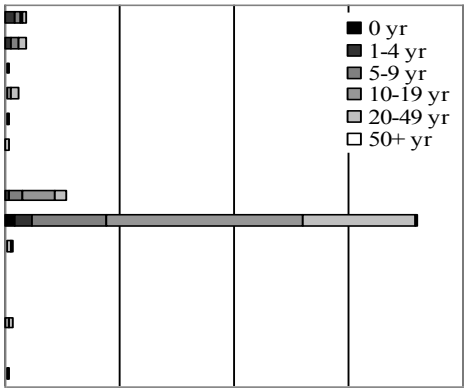


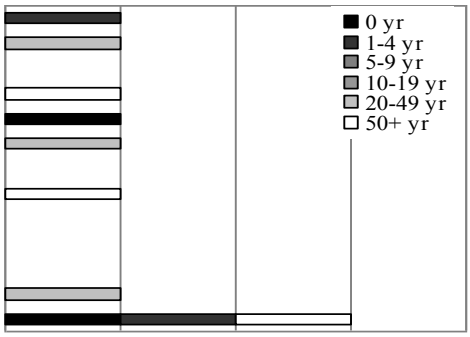
Rubella (Acquired) **ICD9 056** **ICD10 B06**

		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
	2011	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
	2011	0	0	0	0	1	2	3
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
	2011	1	1	0	0	0	1	3

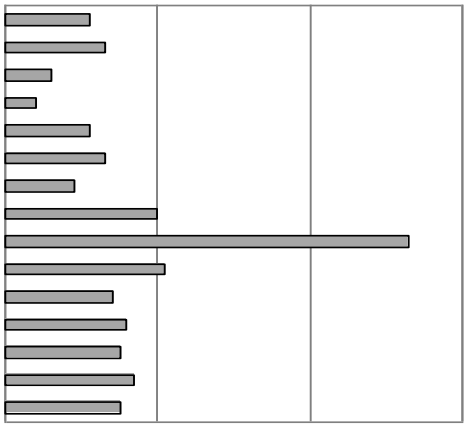
N





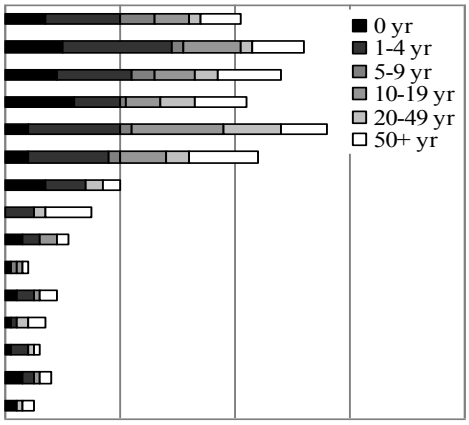


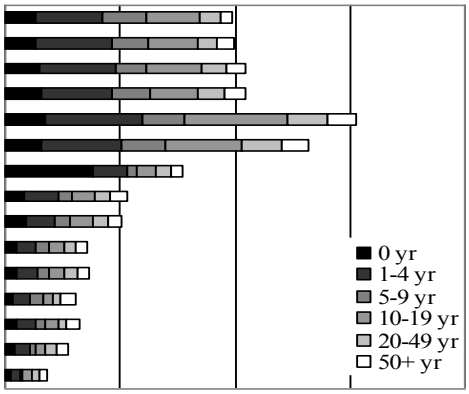
	Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total	N
Isolates 1997	-	-	-	-	-	-	11	
1998	-	-	-	-	-	-	13	
1999	-	-	-	-	-	-	6	
2000	-	-	-	-	-	-	4	
2001	-	-	-	-	-	-	11	
2002	-	-	-	-	-	-	13	
2003	-	-	-	-	-	-	9	
2004	-	-	-	-	-	-	20	
2005	-	-	-	-	-	-	53	
2006	-	-	-	-	-	-	21	
2007	-	-	-	-	-	-	14	
2008	-	-	-	-	-	-	16	
2009	-	-	-	-	-	-	15	
2010	-	-	-	-	-	-	17	
2011	-	-	-	-	-	-	15	

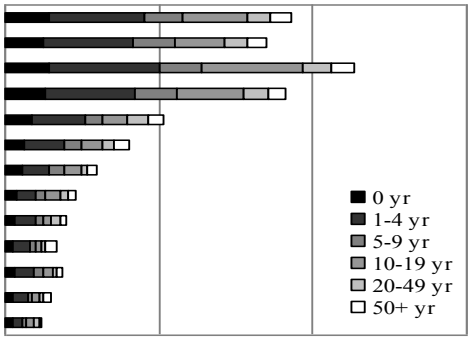


Meningococcal disease **ICD9 036.0-4, 036.8-9** **ICD10 A39**

		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total	N
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	
	2011	2	0	0	0	1	2	5	
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	191	75	22	39	32	27	386	
	2004	42	80	25	50	35	34	266	
	2005	44	71	30	48	30	29	252	
	2006	25	50	20	34	24	27	180	
	2007	26	49	24	32	27	23	181	
	2008	17	47	19	19	17	36	155	
	2009	23	50	18	25	16	28	160	
	2010	22	34	13	21	21	28	139	
	2011	12	23	4	19	17	16	91	
Hospitalisation (036.0, 036.2-	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	
	2011	18	26	10	20	13	9	98	



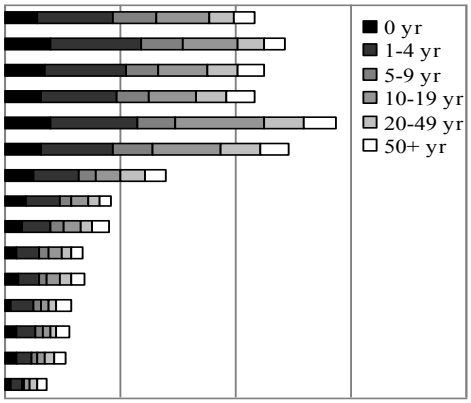




*For some patients the age is unknown.

		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Isolates	1997	71	161	96	114	53	45	539
	1998	100	194	92	117	59	45	607
	1999	86	175	70	109	65	58	563
	2000	79	161	71	102	65	61	539
	2001	98	189	82	193	86	69	717
	2002	79	155	84	148	86	62	614
	2003	61	97	37	53	55	44	347
	2004	47	73	22	40	22	27	231
	2005	37	60	28	40	25	34	224
	2006	25	48	20	29	22	24	168
	2007	28	46	17	28	24	28	171
	2008	14	47	15	17	16	36	145
	2009	23	42	16	16	15	27	139
	2010	23	33	12	17	20	27	132
	2011	14	22	4	14	17	19	90

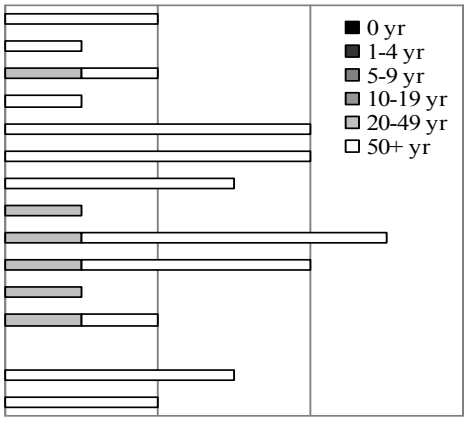
N

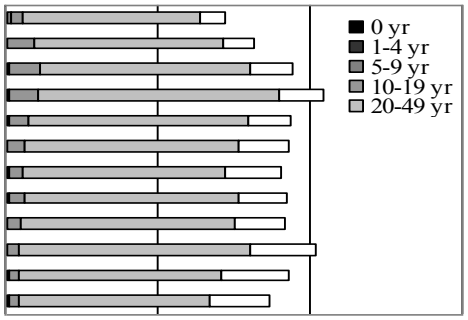


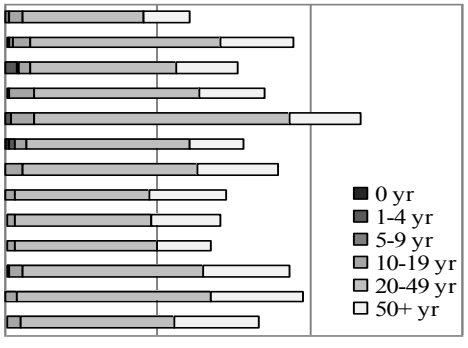
Hepatitis B **ICD9 070.2-3 ICD10 B16 B17.0 B18.0 B18.1**

		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
	2011	0	0	0	0	0	2	2
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	8	12	104	1403	322	1849
	2008	0	9	7	89	1398	336	1839
	2009	0	7	5	81	1519	424	2036
	2010	0	8	11	68	1330	441	1858
	2011	0	8	12	71	1251	390	1732
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
	2011	0	0	1	9	101	55	167

N

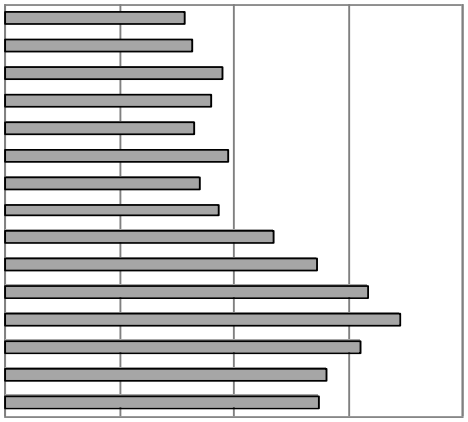




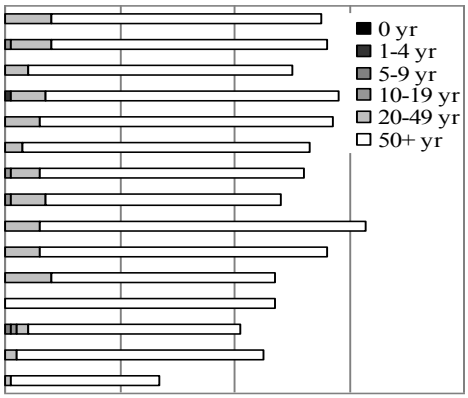
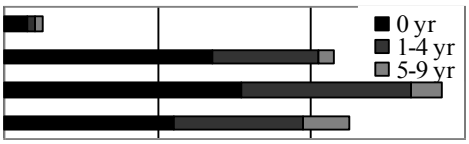
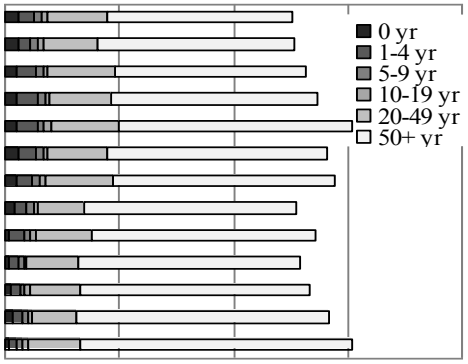
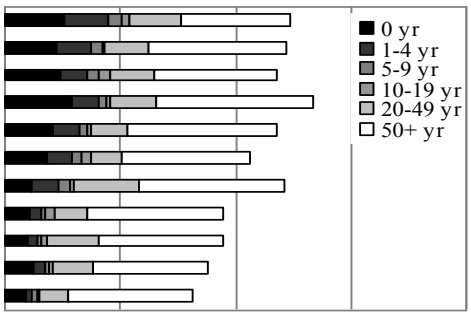


*For some patients the age is unknown.

	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	
2011	-	-	-	-	-	-	1376	



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	N
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	
	2011	0	0	0	0	1	26	27	
Notifications	2008	3	1	1*	-	-	-	5	
	2009	27	15	1*	-	-	-	43	
	2010	31	24	2*	-	-	-	57	
	2011	22	20	3*	-	-	-	45	
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	
	2011	37	57	64	52	452	2369	3033	
Isolates (meningitis)	2001	51	39	11	7	45	95	248	
	2002	45	30	9	2	38	120	244	
	2003	48	24	9	11	37	107	236	
	2004	58	24	6	3	40	137	268	
	2005	42	23	6	4	31	129	235	
	2006	36	22	8	8	28	111	213	
	2007	24	23	10	3	56	127	243	
	2008	21	11	3	8	28	119	190	
	2009	20	8	4	5	45	108	190	
	2010	25	10	4	2	36	98	176	
	2011	18	6	5	1	24	109	163	

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

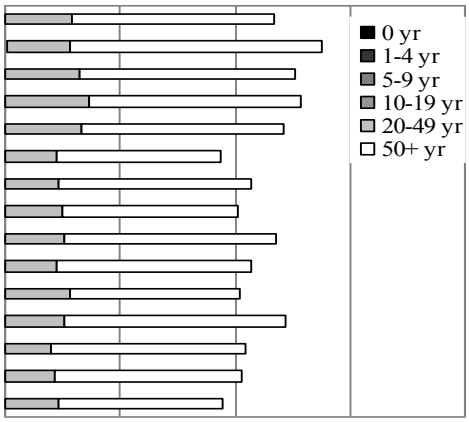
**For some patients the age is unknown.

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

Mortality (Cervical cancer)

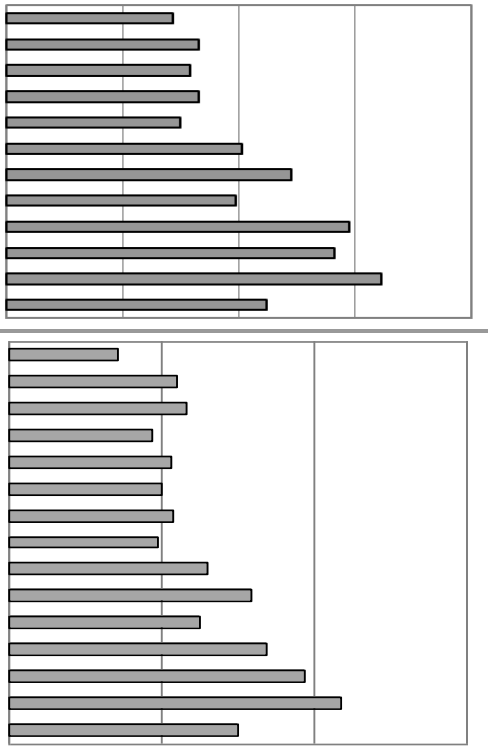
	Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
1997	0	0	0	0	58	176	234
1998	0	0	0	1	56	219	276
1999	0	0	0	0	64	189	253
2000	0	0	0	0	73	185	258
2001	0	0	0	0	66	177	243
2002	0	0	0	0	45	142	187
2003	0	0	0	0	47	167	214
2004	0	0	0	0	49	154	203
2005	0	0	0	0	52	183	235
2006	0	0	0	0	44	170	214
2007	0	0	0	0	57	147	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
2010	0	0	0	0	46	143	189

N



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

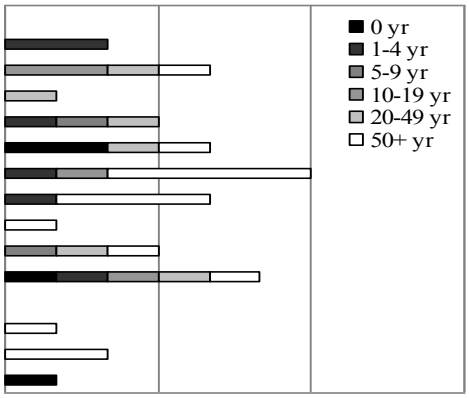
		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Hospitalisations (estimation)	2000	-	-	-	-	-	-	2864
	2001	-	-	-	-	-	-	3312
	2002	-	-	-	-	-	-	3160
	2003	-	-	-	-	-	-	3322
	2004	-	-	-	-	-	-	3000
	2005	-	-	-	-	-	-	4063
	2006	-	-	-	-	-	-	4903
	2007	-	-	-	-	-	-	3948
	2008	-	-	-	-	-	-	5895
	2009	-	-	-	-	-	-	5641
	2010	-	-	-	-	-	-	6442
	2011	-	-	-	-	-	-	4487
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
	2011	-	-	-	-	-	-	1504

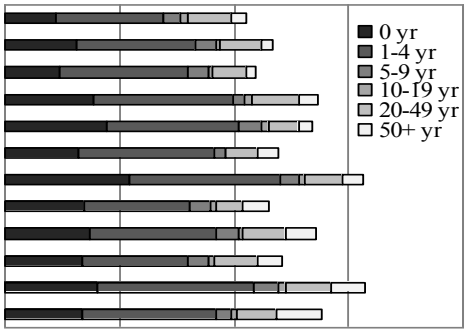


Varicella (Chickenpox) **ICD9 052** **ICD10 B01**

		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
	2011	1	0	0	0	0	0	1
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
	2011	67	118	13	5	34	40	277

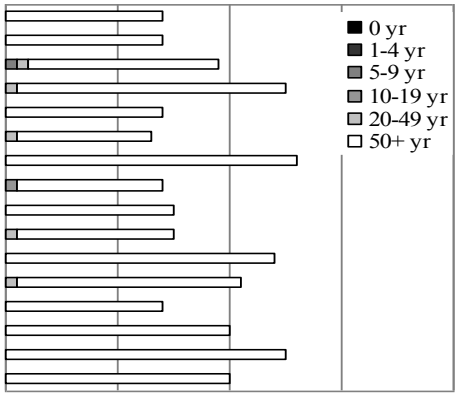
N

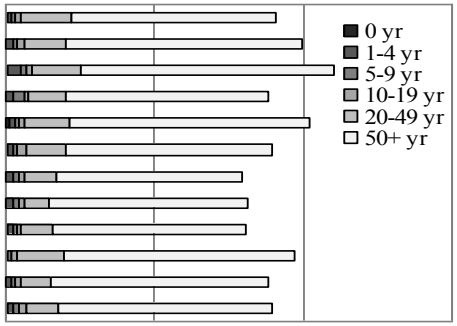




Herpes zoster (Shingles) **ICD9 053** **ICD10 B02**

		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total	N
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	
	2011	0	0	0	0	0	20	20	
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	
	2011	2	9	7	10	43	286	357	

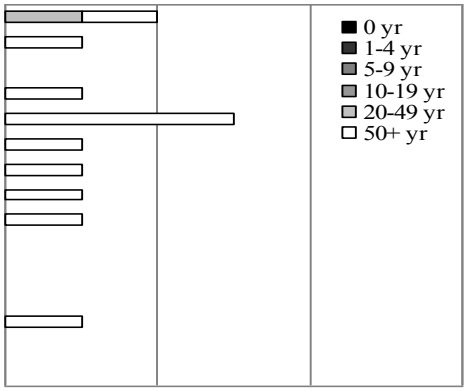


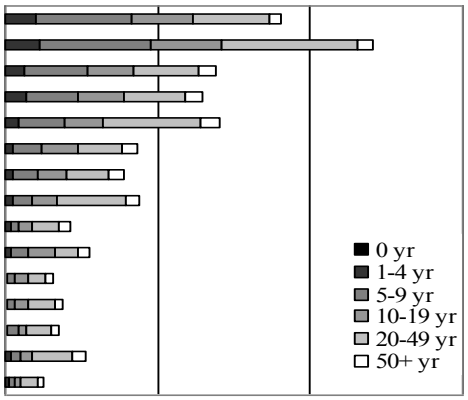


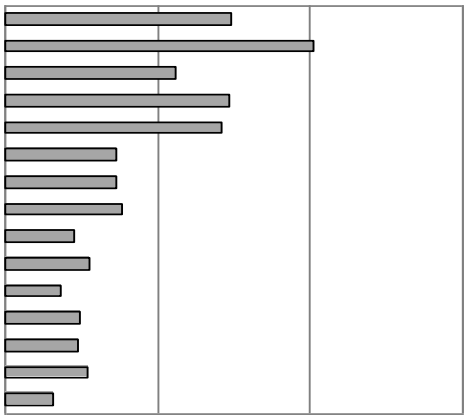
Hepatitis A **ICD9 -** **ICD10 B15**

		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
	2011	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
	2011	0	12	18	22	54	19	125
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
	2011	-	-	-	-	-	-	63

N







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; 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; 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 papillomavirus 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 2012

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 and conjugated *Haemophilus influenzae* type b-vaccin (adsorbed)	Purified pertussis toxoid (PT) 20 µg Purified filamentous haemagglutinin (FHA) 20 µg Purified fimbrial agglutinogens 2 and 3 (FIM) 5 µg Purified pertactin (PRN) 3 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU *Haemophilus influenzae* type b polysaccharide (polyribosylribitol phosphate) 10 µg conjugated to tetanus toxoid (PRP-T) 20 µg absorbed to aluminium phosphate 1.5 mg
0.5 ml	
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
Synflorix/GSK	Pneumococcal polysaccharide serotype $1^{1,2}$ 1 µg
EU/1/09/508	Pneumococcal polysaccharide serotype $4^{1,2}$ 3 µg
Pneumococcal polysaccharide conjugate vaccine (adsorbed)	Pneumococcal polysaccharide serotype $5^{1,2}$ 1 µg Pneumococcal polysaccharide serotype $6B^{1,2}$ 1 µg
0.5 ml	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	

EU/1/00/152	
Diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), inactivated poliomyelitis vaccine and conjugated *Haemophilus influenzae* type b-vaccine (adsorbed) 0.5 ml	Adsorbed diphtheria toxoid > 30 IU Adsorbed tetanus toxoid > 40 IU 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 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 RVG 17672 Mumps, measles and rubella vaccine 0.5 ml	Mumps virus (Jeryl Lynn) > 5000 TCID50 (tissue culture infectious doses) Measles virus (Schwartz) > 1000 TCID50 Rubella virus (Wistar RA 27/3) > 1000 TCID50
Infanrix IPV + Hib / GSK RVG 22123 / RVG 34567 Diphtheria, tetanus, pertussis (acellular component), inactivated poliomyelitis vaccine and conjugated *Haemophilus influenzae* type b-vaccine (adsorbed) 0.5 ml	Adsorbed diphtheria toxoid > 30 IU Adsorbed tetanus toxoid 20 - 40 IU Adsorbed pertussis toxoid (PT) 25 µg Adsorbed filamentous haemagglutinin (FHA) 25 µg Absorbed pertactin (PRN) 8 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU *Haemophilus influenzae* type b polysaccharide 10 µg
Infanrix IPV / GSK RVG 34568 Diphtheria, tetanus, pertussis (acellular component), inactivated poliomyelitis vaccine 0.5 ml	Adsorbed diphtheria toxoid > 30 IU Adsorbed tetanus toxoid > 40 IU Adsorbed pertussis toxoid (PT) 25 µg Adsorbed filamentous haemagglutinin (FHA) 25 µg Absorbed pertactin (PRN) 8 µg 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 EU/1/06/337/001 Mumps, measles and rubella vaccine 0.5 ml	Mumps virus (Jeryl Lynn) > 12,500 TCID50 (tissue culture infectious doses) Measles virus (Enders' Edmonston) > 1000 TCID50 Rubella virus (Wistar RA 27/3) > 1000 TCID50
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.*

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