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

The National Immunisation Programme in the Netherlands

Developments in 2013

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Colophon

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

Report prepared by:
N. Alberts[7,8], H.G.A.M. van der Avoort[1], W.A.M. Bakker[2], G.A.M. Berbers[1], R.S. van Binnendijk[1], J.A. Bogaards[1], P. Bruijning-Verhagen[1], A. Buisman[1], J. Cremer[1], R. Donken[1], G.A. Donker[5], E. Duizer[1], R. Eilers[1], K.E.M. Elberse[1], C.A.C.M. van Els[1], A. van der Ende[6], I.H.M. Friesema[1], S. Gouma[1], M.C.H. Govers[4], S.J.M. Hahné[1], I.A. Harmsen[1,] P. Jochemsen[1], P. Kaaijk[1], J.M. Kemmeren[1], A.J. King[1], F.R.M. van der Klis[1], T.M. Schurink-van 't Klooster[1], M.J. Knol[1], F. Koedijk[1], E.A. van Lier[1], S.J.M. Leeman[4], A.K. Lugner[1], W. Luytjes[1], N.A.T. van der Maas[1], L. Mollema[1], M. Mollers[1], F.R. Mooi[1], D.W. Notermans[1], W. van Pelt[1], F. Reubsaet[1], N.Y. Rots[1], W.L.M. Ruijs[1], J. Sane[1], L. Spanjaard[6], J.E. van Steenbergen[1], I. Stirbu-Wagner[5], A.W.M. Suijkerbuijk[2], J. Veldwijk[3], L.P.B. Verhoef[1], M.A. Vink[1], O. Visser[9], J.A. van Vliet[1], H.J. Vriend[1]

[1] Centre for Infectious Disease Control, RIVM
[2] Institute for Translational Vaccinology (Intravacc)
[3] Sector for Public Health and Care, RIVM
[4] Communication department, RIVM
[5] Netherlands Institute for Health Services Research, NIVEL
[6] Reference Laboratory for Bacterial Meningitis, AMC
[7] Municipal Health Service (GGD), Amsterdam
[8] Centre for Infection and Immunity Amsterdam, AMC
[9] Academic Collaborative Centre AMPHI, Radboud UMC

Contact:
H.E. de Melker
Centre for Epidemiology and Surveillance of Infectious Diseases
hester.de.melker@rivm.nl

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Rapport in het kort

Het Rijksvaccinatieprogramma in Nederland
Ontwikkelingen in 2013

In 2012 was er een grote kinkhoestepidemie in Nederland. Het betrof voornamelijk kinderen tussen 0 en 2 maanden oud, kinderen van 8 jaar en ouder, en volwassenen. Het aantal kinkhoestmeldingen was in de eerste helft van 2013 laag. De uitbraak van de bof die eind 2009 begon, is in 2013 verminderd, al verspreidt het virus zich nog wel in Nederland.
Daarnaast is er sinds mei 2013 een uitbraak van mazelen in Nederland, vooral onder orthodox-gereformeerden met een lage vaccinatiegraad. Verwacht wordt dat de uiteindelijke omvang van deze uitbraak groter zal zijn dan de vorige in 1999/2000.

Dit blijkt uit het jaaroverzicht van het RIVM over de mate waarin ziekten voorkomen waartegen gevaccineerd wordt via het Rijksvaccinatieprogramma (RVP), en de ontwikkelingen daarin. Het geeft ook inzicht in de vaccins die zijn gebruikt en welke bijwerkingen daarbij optraden. Ontwikkelingen over nieuwe vaccins, die eventueel in de toekomst in het RVP worden opgenomen, zijn ook beschreven. Doordat de vaccinatiegraad al vele jaren hoog is, krijgen weinig mensen de ziekten waartegen via het RVP wordt gevaccineerd. Het vaccinatieprogramma is bovendien veilig, waarbij er relatief weinig bijwerkingen voorkomen die doorgaans niet ernstig van aard zijn. Wel blijft voor een optimaal vaccinatieprogramma continue monitoring van effectiviteit en bijwerkingen nodig.

Andere ontwikkelingen
Uit het overzicht blijkt ook dat er tijdens de eerste weken van de mazelenepidemie ook een kleine uitbraak van rodehond heeft plaatsgevonden op een orthodox-gereformeerde school. Dit veroorzaakte het grootste aantal zieken door rodehond sinds 2004/2005.

In Syrië en Israël is het poliovirus verspreid. In Nederland zijn er tussen medio 2012 tot 1 november 2013 geen gevallen van polio gemeld. Verder zijn er in 2013 in Europese landen enkele gevallen van meningokokken C gerapporteerd onder mannen die seks hebben met mannen (MSM). In Nederland is dat onder mannen die tot deze risicogroep kunnen behoren niet gemeld.

Effectiviteit pneumokokkenvaccin
Uit onderzoek naar de effectiviteit van het pneumokokkenvaccin blijkt dat het vaccin evenveel bescherming biedt als het aantal prikmomenten wordt verlaagd. De Gezondheidsraad heeft geadviseerd om minder prikken in het prikschema op te nemen.

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

Abstract

The National Immunisation Programme in the Netherlands
Developments in 2013

In 2012, a large pertussis outbreak occurred in the Netherlands. The highest incidences were among infants aged 0–2 months, children of eight years and older, adolescents and adults. The number of pertussis notifications in the first six months of 2013 was found to be low. The mumps outbreak that started among students in late 2009 diminished in 2013, but there are still indications of endemic transmission.
In addition, an outbreak of measles started in May 2013 among the Reformed Orthodox population, who have low vaccine coverage. The outbreak is expected to continue with a final size that may exceed that of the 1999/2000 outbreak.

This information is included in this annual report of the National Institute for Public Health and the Environment (RIVM) which gives an overview of how often diseases included in the National Immunisation Programme (NIP) occur and presents developments in the NIP. The report also indicates which vaccines are used and which adverse events were reported after vaccination. Developments with regard to potential target diseases for vaccines are also included. The participation level in the NIP has been high for many years, resulting in low incidences of most target diseases. The programme is also safe with relatively few side effects reported, and these are usually mild and transient. For an optimal programme, continuous monitoring of effectiveness and safety remains necessary.

Other developments
During the first weeks of the measles epidemic in June 2013, a small and restricted rubella outbreak was identified at an Orthodox school. This was the largest rubella outbreak since 2004/2005.

In Syria and Israel, respectively, cases of poliovirus and the transmission of poliovirus were identified in 2013. In 2012 and 2013 (at 1 November), no cases of poliomyelitis were reported in the Netherlands.

In June 2013, a meningococcal C outbreak among men who have sex with men (MSM) was reported in Europe. No meningococcal serotype C cases among men that may belong to this risk group were reported in the Netherlands.

Effect of pneumococcal vaccine
Research showed that the protection of the pneumococcal vaccine is similar in a schedule with a reduced number of doses compared to the current schedule. Therefore, the Dutch Health Council advised on 27 November 2013 in favour of a schedule with a reduced number of doses.

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

Preface

This report presents an overview of the developments in 2013 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 target diseases, for which a vaccine is available are described. The diseases are: rotavirus infection, varicella zoster virus infection (VZV), meningococcal serogroup B and hepatitis A infection. This report also covers meningococcal non-serogroup B and C types to facilitate the study of trends in these serogroups. In addition, data on vaccines for infectious diseases tested in clinical trials that are relevant for the Netherlands are included in this report.

The report is structured as follows: Chapter 1 gives a short introduction. In Chapter 2 the surveillance methods used to monitor the NIP are described. Recent results on vaccination coverage are discussed in Chapter 3 and public acceptance of vaccination and communication of the NIP in Chapter 4. Chapter 5 focuses on the 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 the NIP are mentioned. The results of ongoing studies, together with the planning of future studies and international developments are described. Chapter 6 describes new target diseases, which are under consideration for inclusion in the future NIP. Finally, in Chapter 7 vaccines for infectious diseases which are being tested in clinical trials and are relevant for the Netherlands are described. In Appendix 1 mortality and morbidity figures from 1997 onwards from various data sources are reported.

Contents

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 potential target diseases for which a vaccine is available (rotavirus, varicella zoster virus (VZV), hepatitis A, 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 and pneumococcal disease, at the ages of 2, 3, 4 and 11 months. Subsequently, vaccines against MMR and meningococcal C disease are administered simultaneously at 14 months. DTaP-IPV is then given at 4 years and DT-IPV and MMR at 9 years. Vaccination against HPV is offered to 12-year-old girls.

Dutch Caribbean
Experts from the Dutch Caribbean and the RIVM collaborate on harmonisation of the immunisation programme on these islands with the Dutch NIP. As of 1 January 2013, Saba and St Eustatius had added vaccination against pneumococcal disease, meningococcal C disease and HPV. Bonaire started arranging the replacement of the oral polio vaccine with an inactivated vaccine.

Vaccination coverage
The participation rates for all vaccinations (except for HPV) included in the NIP are high at between 92% to 99%. Furthermore, there are fewer municipalities with one or more vaccination percentages below the lower limit of 90% than in earlier report years. The immunisation coverage for three doses of the HPV vaccine among adolescent girls was 58%.

Diphtheria
In 2012, one case of diphtheria was reported in the Netherlands. In 2013 until September 15, no diphtheria cases were reported.

Pertussis
In 2012, a large pertussis epidemic occurred with the highest number of notified cases since the introduction of notification in 1976. Data on consultations by general practitioners (GPs) and hospitalisations in 2012 also showed an increase compared to earlier years. In the first six months of 2013, the incidence of pertussis notifications was found to be low. Pertussis outbreaks continue to be reported throughout the world.
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 of the components of pertussis vaccines.
The main focus of pertussis vaccination is to prevent severe pertussis in young, not yet fully vaccinated infants. Maternal immunisation is recommended in several countries to better protect young, not yet fully vaccinated, infants.

Tetanus
In 2012, two cases of tetanus were reported; one case was vaccinated, the other had an unknown vaccination status. In 2013 (to 5 September), no cases of tetanus were reported.

Low numbers of tetanus cases are reported almost every year, mostly among the elderly. Some of these cases visited a physician and did not receive tetanus post-exposure prophylaxis, indicating that Dutch Health Council recommendations on tetanus post-exposure prophylaxis are not always properly followed. In the Netherlands, research among GPs and emergency departments showed that almost all use guidelines for tetanus post-exposure prophylaxis. Strict adherence to the recommendations of the Dutch Health Council is low. More than half of GPs use the guidelines of the Dutch College of GPs, which are more restrictive, i.e. limiting tetanus post-exposure prophylaxis to tetanus-prone wounds.

Poliomyelitis
In 2012 and 2013 (as at 1 November) no cases of poliomyelitis were reported in the Netherlands, in spite 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.
Since February 2013, wild poliomyelitis virus type 1 (WPV1) has been detected in Israel in 91 sewage samples, indicating country wide transmission. No cases of paralytic polio have yet been identified. Travel to Israel by unvaccinated people is strongly discouraged. Travel organisations are regularly informed of vaccination recommendations for travellers to Israel. Cases of poliomyelitis have been confirmed in Syria in October 2013, where almost all infrastructure for public health and medical services is destroyed during the continuing civil war. The influx of Syrian refugees to the Netherlands and the number of Dutch people visiting religious sites in Israel, give cause for assessing the risk of reintroduction of polio in the Netherlands.
No wild poliovirus type 3 was detected globally by acute flaccid paralysis (AFP) or environmental surveillance in 2013. The last report of type 3 polio virus came from an AFP case in Nigeria in November 2012.

***Haemophilus influenzae* serotype b (Hib) disease**
There were no significant changes in the number of invasive disease cases caused by *Haemophilus influenzae* serotype b (Hib) in 2012 and 2013 in the Netherlands. Furthermore, no increase in vaccine failure against invasive Hib disease has been seen in recent years.

Mumps
The mumps outbreak which started among students in late 2009 continued throughout 2010–2012 with clear seasonality, peaking in March each year. There was a shift in outbreak strains, the predominant outbreak strain in 2010 being G5 variant 1 and the strain which predominated in 2011 and 2012 being G5 variant 2. In 2013, mumps outbreaks diminished, but there is still consistent reporting of mumps at rates higher than before 2010, indicating that there is still endemic transmission. This is consistent with the molecular detection of both G5 variants in most cases.

Measles
During 2012, ten measles cases were reported, eight of which had a documented origin of infection outside the Netherlands. The two remaining cases resulted in an indigenous measles incidence of 0.1/1,000,000, which is well below the WHO elimination target (1 per 1,000,000 population).
In May 2013 an outbreak of measles started among the Reformed Orthodox population, which has low vaccine coverage. Up to 2 October 2013, 1646 cases were reported. Due to the accumulation of susceptibles in the unvaccinated

population since the previous measles outbreak in 1999/2000, reflected in seroprevalence results (PIENTER-2), the current outbreak may exceed the previous one, when over 3,200 cases were reported.

Rubella
The rubella incidence during 2012 was very low (1 case; 0.1/million population). During the first weeks of the measles epidemic, in June 2013, a small and restricted rubella outbreak was identified at an orthodox school in the 'Hollands Midden' region, where 54 related cases were reported. This is nevertheless the largest rubella outbreak since 2004/2005. This rubella outbreak appears to have been caused by the same genotype 2B rubella virus as was identified for a large Polish rubella outbreak in 2013, but there are no epidemiological data to support a direct link. Genotype 2B is assumed to be the most prevalent one in Europe on the basis of rubella reports in Europe in 2012.

Meningococcal serogroup C disease
The incidence of meningococcal serogroup C (MenC) disease has greatly decreased since the introduction of vaccination in 2002.
An immunogenicity study among children vaccinated against MenC during the catch-up campaign showed that nine years after vaccination 45% of 15-year olds had protective antibody levels, 34% of 12-year olds and only 19% of 10-year olds. If MenC circulation increases, the need for a MenC booster in adolescents might be considered given the observed waning antibody titers against MenC.
In June 2013, a MenC outbreak among men who have sex with men (MSM) was reported in Europe with a possible link to an outbreak in the US. No MenC cases among men older than 16 years were observed in the Netherlands. Since August 2013, the reporter of a case has been specifically asked whether the case belongs to the MSM group.

Hepatitis B
The incidence of acute hepatitis B virus notifications, which had been decreasing since 2004, increased slightly in 2012 compared with 2011. Among men, sexual contact with men remained the most frequently reported risk factor. Molecular surveillance suggests that transmission of the clonal genotype A strain, which has been detected since the start of molecular surveillance, continues.

Pneumococcal disease
The introduction of vaccination against pneumococcal disease in the NIP in 2006 has led to a considerable reduction in the number of cases of invasive pneumococcal disease (IPD) caused by the serotypes included in the 7-valent pneumococcal conjugated vaccine (PCV7) in all age groups. However, the reduction in IPD caused by PCV7 serotypes has been partly counterbalanced by an increase in non-PCV7 serotype IPD. The overall incidence decreased for 0–4-year-olds and adults over 65 years of age but remained more or less stable in other age groups. A decrease in IPD caused by the three additional serotypes included in PCV10 (implemented in May 2011 in the NIP) was seen among 0–1-year-old children.
An immunogenicity study (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 schedules. Importantly, after the booster dose at 12 months, all four immunisation schedules showed similar and protective antibody concentrations, showing that a reduced schedule could be considered.

The PIEN study comparing PCV10 and PCV13 showed that antibody levels were generally higher for PCV10 before the booster dose and higher for PCV13 after the booster dose.

Human papillomavirus (HPV)
Slightly increasing incidences of HPV-associated cancers have been found in the Netherlands in the last decade.
The reporting rate of adverse events in 2012 was clearly higher than the reporting rate in 2011, but it was comparable with the reporting rate in 2010. No statistically significant association between HPV vaccination and migraine was found using different kinds of analysis, although numbers were low.
The cumulative incidence of HPV among vaccinated and unvaccinated girls in a cohort study among girls eligible for HPV vaccination at 36 months was 23.1% for any HPV type and 14.2% for high risk HPV types. The cumulative persistence at 36 months was 5.8% for any HPV and 2.8% for high risk HPV. A study among visitors to STI clinics showed that HPV DNA positivity and HPV antibody seropositivity were higher in women than in men. The association between type-specific DNA and serum antibodies was similar across gender. It was estimated by mathematical modelling that the HPV-related cancer burden among males was reduced by approximately one-third at the current vaccine uptake of 60%, and by two-thirds at a constant 90% uptake among pre-adolescent girls.
In some countries early effects of the introduction of HPV vaccination become visible, i.e. reduction in genital warts and high-grade cervical abnormalities.

Rotavirus
After a rise in the incidence of rotavirus-associated gastroenteritis seen in the Netherlands in the last few years, the decrease in 2011 continued in 2012. In 2012, G1P[8], G9P[8], G3P[8] and G4P[8] were most commonly found in the Netherlands.

Varicella zoster virus (VZV) infection
No striking changes occurred in the VZV epidemiology in the Netherlands in 2012. The Integrated Primary Care Information (IPCI) databases showed that complications were recorded in 21% of the varicella cases that consulted a GP and that these complications were most often mild. Referral to secondary health care was low (2%).

Hepatitis A
In 2012, the number of hepatitis A infections (121 cases) remained low compared with previous years. Forty percent of the Dutch cases were reported to be travel-related, most of them having visited Morocco.

Meningococcal serogroup B disease
The incidence of meningococcal B (MenB) disease among 0–1-year-olds increased in 2012, whereas the total number of MenB cases was comparable to 2011. In 2013 (until July), a small increase in MenB disease was observed. The proportion of the dominant PorA genosubtype P1.7-2,4 in serogroup B isolates had decreased from 2000 to 2012. The dominant FetA type F1-5, which had been decreasing until 2011, increased again in 2012.
In January 2013, the European Commission approved the meningococcal B vaccine Bexsero (Novartis) for use in individuals from two months of age. On the basis of an unfavourable assessment of cost-effectiveness, the UK's Joint Committee on Vaccination and Immunisation (JCVI) decided not to implement the 4CMenB (Bexsero) vaccine in the NIP in the UK.

Meningococcal non-B and non-C disease
In 2012, of 95 meningococcal cases, 16 were non-serogroup B and C. After a decrease in incidence of meningococcal serotype Y disease in 2012, an increase was observed in 2013 (until July).

Other possible future NIP candidates
Vaccines against HIV, hepatitis C virus, *Clostridium difficile*, *Staphylococcus aureus*, *Pseudomonas*, Group B Streptococcus and Cytomegalovirus have reached the clinical testing phase. At present none of the respiratory syncytial virus (RSV) vaccine concepts has entered advanced stages of clinical development.
New vaccine concepts against tuberculosis are under development, including modification of the existing vaccine, BCG.
Limitations and failed public acceptance of a human vaccine comprising the outer surface A (OspA) lipoprotein of *Borrelia burgdorferi*, led to its demise. However, current research has reopened doors to new strategies for protection against Lyme disease.

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

1 Introduction

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

Vaccination of a large part of the population of 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 1 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 whose mother has tested positive for HBsAg.

[b] Only for girls; three doses: at 0 days, 1 month and 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 people aged 60 years and over and people in the Dutch population with an increased risk of morbidity and mortality following an influenza virus infection. Furthermore, vaccination against tuberculosis is offered to children of immigrants from high-prevalence countries. For developments on influenza and tuberculosis we refer readers to the reports of the Centre for Infectious Disease Control (CIb), the Health Council and the KNCV Tuberculosis Foundation [1-4]. Besides vaccination against HBV included in the NIP, an additional vaccination programme targeting groups particularly at risk of HBV due to sexual behaviour or profession is in place in the Netherlands.

In 2010, Bonaire, Sint Eustatius and Saba (BES) became Dutch municipalities, together called the Dutch Caribbean. This means that the Ministry of Health, Welfare and Sports is responsible for public health on these islands. The Dutch Health Council advised that the immunisation programme in the Dutch Caribbean should be harmonised with the European Dutch Immunisation programme meaning that three vaccinations should be added: against

pneumococcal disease, meningococcal C disease and cervical cancer (HPV vaccine) [5]. Following this advice all three islands have made an implementation plan. The two smallest islands, Saba and St Eustatius, had added these three vaccinations into their programmes by 1 January 2013. Bonaire, which added vaccination against pneumococcal disease in January 2012, is currently making arrangements for the replacement of the oral (live attenuated) polio vaccine with an inactivated vaccine that requires intramuscular administration and for the implementation of the MenC vaccine. Both will be effective from January 2014.
A limitation is the lack of data on the incidence of infectious diseases on these islands, which have a too small population for reliable estimates. The need for epidemiological data to evaluate the current vaccination programme and to inform future programme changes has been stressed [5].

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 in non-immunised individuals. To achieve herd immunity, a high general vaccination rate is necessary. If this second strategy is not feasible either, the third option is to protect as many individuals as possible.
In the previous century, smallpox was eradicated and today the public health community is committed to the WHO target of eradicating 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 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 for identifying risk groups, tracing disease sources and achieving elimination and eradication. Surveillance provides information to the Health Council, the Ministry of Health, Welfare and Sports (VWS) and other professionals to enable them to decide or 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.
To understand the overall impact of vaccination on the health of a population, at a time when the primary infections targeted by these vaccinations have become rare, it is essential that reliable and rapid data are generated from post-marketing surveillance and studies. While pharmaceutical companies are by law obliged to conduct such studies, outcomes may not be fully and rapidly available for public health decisions. The Innovative Medicines Initiative of the EU has therefore commissioned a five-year project in which the pharmaceutical industry has to work with the public sector (public health, academia, regulators) to develop a framework for such studies to ensure that reliable data on the benefits and risks of vaccination is generated and communicated rapidly. The RIVM is one of the public health partners in this project (ADVANCE).

2 Surveillance methodology

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2.1 Disease surveillance

For all the 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

Statistics Netherlands (CBS) registers mortality data from death certificates on a statutory basis. The registration specifies whether it concerns a natural death, a non-natural death or a stillborn child. In the event of natural death, the physician should report the following data:

1. The illness or disease which has led to death (primary cause);
2. a. any complication, directly related to the primary cause, which has led to death (secondary cause);
   b. additional diseases and specifics present at the moment of death, which have contributed to the death (secondary causes).

The CBS codes causes of death according to the International Classification of Diseases (ICD). This classification is adjusted every ten years or so, which have 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 have been notifiable during the entire period. See Table 2 for the period of notification for each disease [6].

Table 2 Periods of statutory notification for vaccine-preventable diseases included in the current 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 passed which required the notification of all NIP-targeted diseases (except HPV). Since that time physicians, laboratories and

heads of institutions have to report 42 notifiable infectious diseases, instead of 36, to the Public Health Services (Wet Publieke Gezondheid).
There are four categories of notifiable disease. Diseases in category A have to be reported directly by telephone following a laboratory-confirmed diagnosis. Diseases in 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 last three categories, different intervention measures can be enforced to prevent the spread 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 Register (LMR) receives the discharge diagnoses of all patients who are admitted to hospital. Outpatient diagnoses are not registered. Diseases, including all NIP-targeted diseases, are coded as the main or subsidiary diagnosis according to the ICD-9 coding system. Until 2010, the LMR was managed by the research institute Prismant; since 2011, Dutch Hospital Data has managed 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 susceptible 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 example, tetani cases are sometimes incorrectly registered as tetanus [9] and cases of post-poliomyelitis syndrome are sometimes classified as acute poliomyelitis, even though these occurred many years ago. Furthermore, cases of acute flaccid paralysis (AFP) with other causes than poliovirus infection are sometimes 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 be diagnosed only by laboratory tests [10]. However, limited information on patients is registered and, in many cases, laboratory confirmation is not sought for self-limiting vaccine preventable diseases. The different laboratory surveillance systems for diseases targeted by the NIP are outlined below.

2.1.3.1 Netherlands Reference Laboratory Bacterial Meningitis

The Netherlands Reference Laboratory for Bacterial Meningitis (NRBM) is a collaboration between the 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 to NIP surveillance.

2.1.3.2 Virological laboratories

Each week, virological laboratories, which are part of the Dutch Working Group for Clinical Virology, send positive results of virological diagnostics to the 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 the presence of 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 an important part of information gathering on the emergence of (sub)types, which may be more virulent or less effectively controlled by vaccination. It is also a useful tool for improving insight into transmission dynamics.

2.3 Immunosurveillance

Monitoring the seroprevalence of all NIP-targeted diseases is a way to gather age- and sex-specific information on immunity to 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 in 2006–2007 [12] (n_{blood}=7,904). Oversampling of people living in regions with low vaccine coverage and 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 into the effectiveness of the NIP. Furthermore, this information can identify groups with low vaccine coverage, who are at increased risk of contracting one of the NIP-targeted 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 operated by the RIVM until 2011. An aggregated analysis of all reported adverse events following immunisation (AEFI) was published annually. The last report, for 2010, also contains a detailed description of the methodology used and a review of trends and important findings over the previous 15 years [14]. From 1 January 2011 this enhanced spontaneous reporting system of AEFI was taken over by the Netherlands Pharmacovigilance Centre (Lareb). Detailed information is available at www.lareb.nl.
In view of 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 AEFIs.
In addition, the CIb performs systematic studies to monitor the safety of the NIP, e.q. questionnaire surveys and linkage studies between different databases.

2.6 Vaccine effectiveness

After implementation, vaccine effectiveness (VE) can be routinely 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

In addition, several study designs, including case-control and cohort studies, can be used to assess VE after implementation [15].

3 Vaccination coverage

E.A. van Lier

As in previous years, in the reporting year 2013, the participation rate at national level for vaccinations included in the National Immunisation Programme (NIP) is high, at 92% to 99% [16]. The exception is the participation rate for HPV vaccination against cervical cancer, which increased by 2% over last reporting year, to 58%.
The participation rate for pneumococcal vaccination (95%) and the second MMR vaccination for 9-year-olds (93%) also increased slightly over last year (both by 0.3%). The latter finding is important because of the aim of the World Health Organization (WHO) to eliminate measles worldwide. Furthermore, there are fewer municipalities with one or more vaccination percentages (HPV and hepatitis B are excluded because not all children were eligible for these vaccinations at the time of analysis) below the lower limit of 90% (80 municipalities in reporting year 2013 versus 90 municipalities in reporting year 2012 and 107 municipalities in reporting year 2011).

The immunisation of premature children deserves special attention. Because their immunisation is less timely, they are at increased risk of diseases against which the NIP offers protection [17].

Through voluntary vaccination, high vaccination coverage is reached in the Netherlands. High levels of immunisation are necessary in order to protect as many people individually as possible. For most target diseases in the NIP it is also important to protect the population as a whole against outbreaks. This protection is achieved through herd immunity.

Table 3 Vaccination coverage per vaccine for age cohorts of newborns, toddlers, schoolchildren, and adolescent girls in 2006-2013

	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	94.8
2013	2010	95.5	96.1	95.1	96.0	96.1	92.8	98.5

	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
2013	2007	92.3	2002	93.1	92.9	1998	58.1

*Vaccination coverage is assessed at the ages of 2 years (newborns), 5 years (toddlers), 10 years (schoolchildren) and 14 years (adolescent girls).
**Only for newborns born on or after 1 April 2006.
***Two MMR vaccinations (in the past 'at least one MMR vaccination' was reported).
[a] Children at least one of whose parents was born in a country where hepatitis B is moderately or highly endemic.
[b] Children whose mother has tested positive for HBsAg.

4 Acceptance of vaccination and communication of NIP

L. Mollema, I.A. Harmsen, M.C.H. Govers, S.J.M. Leeman, E. A. van Lier, J.E. van Steenbergen, J.A. van Vliet, W.L.M. Ruijs, J. Veldwijk, O. Visser, R. Eilers, N. Alberts, H.E. de Melker

4.1 Acceptance of vaccination

Average vaccination coverage in the Netherlands is high (95%). It is essential that this high vaccination coverage is sustained. Therefore, the RIVM aims to monitor the trust in vaccination among the public and professionals. Various studies are performed to obtain insight into factors that are associated with trust in the vaccination programme in general and in specific vaccinations. This information can be used to strengthen communication about the NIP, thereby enabling parents and children to make an informed decision whether or not to be vaccinated. A brief description of the various studies is given below.

4.1.1 Monitoring system for acceptance of vaccination

In the interest of the development of a monitoring system various studies have been conducted, such as focus group studies with a diverse group of parents and child vaccine providers (CVPs). Additionally, in 2013 a study on parental information-seeking behaviour with regard to childhood vaccination was performed. This study showed that almost half of parents (46%) searched for information other than that contained in the regular information brochure and 13% of parents indicated that they lacked some information, particularly about the side effects of vaccines. Parents' intention to search for information was influenced by a positive attitude and the perceived social norm of information-seeking behaviour.

Furthermore, questionnaires were sent to parents with at least one child under four years old in order to determine the most important factors associated with parents' intention to have their child(ren) vaccinated or not. Results will become available in 2014.

Another study that is ongoing is the analysis of information in online (social) media about measles in particular (in the light of the ongoing measles outbreak in the Netherlands) and vaccination in general, to ascertain the most discussed topics in social media and the sources of the messages, and also to find out how the results can be used to improve the monitoring system.

At the end of 2013, CVPs will receive a questionnaire designed to gain insight into their experience within the NIP, the parents that visit the child welfare centres (CWC), and how satisfied the CVPs are with the current NIP. The information from these studies will be used to set-up a monitoring system on vaccine acceptance and trust in the NIP among parents and CVPs in the Netherlands.

4.1.2 Under-vaccinated groups in Europe

In three European countries, including the Netherlands, a study among under-vaccinated groups (UVGs) has been performed. This was part of an EU-funded project on effective communication in outbreak management: the development of an evidence-based tool for Europe (E_com@eu). The aim was to give advice on how to communicate with under-vaccinated groups in outbreak situations. First, an overview was given of the under-vaccinated groups in the Netherlands, Romania and Portugal and of the determinants of vaccination decision-making. For the determinants that are most common among under-vaccinated groups,

communication strategies were suggested. Second, a media analysis was performed to estimate the possible influence of these under-vaccinated groups on the population in the media.
The results of the media analysis showed that vaccine resistance does not have a significant presence in the mainstream media. It also showed that in the Netherlands opponents to vaccination for religious reasons (e.g. inhabitants of the Bible Belt) are not visible on the Internet. Furthermore, the anthroposophical websites did not fundamentally oppose vaccination, but rather tried to inform readers. The dominant people online were followers of an alternative lifestyle, concerned mothers and people inclined to conspiracy theories.
The study suggests that one of the communication strategies for stimulating informed decision-making could be to develop decision guides for UVGs focusing on their specific dilemmas. These guides should include frequently asked questions with answers, and illustrations of risks and consequences framed in ways that are relevant to and understandable by UVGs. These guides should be made available in paper form and through digital technology such as websites and (cross-platform) apps. A good example of such a communication strategy is the brochures for Reformed Orthodox individuals to help them to make a considered decision for or against vaccination based on religious arguments rather than medical arguments, which are less important to this group. The brochures are available from http://www.academischewerkplaatsamphi.nl/news/4323/Brochures-over-vaccinatie-reformatorische-gezindte/7050.

4.1.3 *Dialogue between health professionals and parents*

A qualitative ethnographic study was performed on the interaction between professionals and parents in the consultation room of CWCs. Observations in ordinary as well as anthroposophical CWCs, and interviews with CVPs and parents have been carried out. Three styles of communication about childhood vaccination were observed: (1) 'steering and persuading' – a style that implies that professionals highly identify themselves with the NIP and prevent discussion with parents about the programme; (2) 'inviting and convincing' – a style in which professionals invite parents to agree with vaccination by giving an opportunity for questions and discussion; (3) 'deliberating' – a style which shows that professionals are prepared to discuss parents' doubts, wishes and needs. Styles 1 and 2 were present in ordinary CWCs. Style 3 was observed in anthroposophical CWCs. It was concluded that in the daily practice of Dutch ordinary CWCs parental feedback on vaccination by means of communication can be improved. How this might be done needs further research.

4.1.4 *Intention to new vaccines*

Questionnaire data among parents with at least one child under four years old showed that they believe varicella to be in general a relatively mild disease. Only 28% of the parents surveyed had a positive intention to accept a vaccine against varicella within the NIP. Questionnaire data among health professionals showed that 21% were in favour of offering varicella vaccination to all children, while 72% would restrict it to specific risk groups.

Results from another study showed that the vast majority of parents reported that they intended to vaccinate their new-born babies against rotavirus if such a vaccine would become available. Preliminary results from a discrete choice experiment reveal that the potential vaccination coverage for a rotavirus vaccine ranges from 21% to 88% for different vaccine scenarios and implementation strategies, depending on vaccine effectiveness, protection duration, frequency of severe side effects, location of administration and out-of-pocket cost. Thus when vaccine effectiveness is low, the protection duration is short, severe side effects

occur frequently and the own costs are high, vaccination coverage will be lowest. In 2014, further data concerning the relative importance of these determinants will become available.

4.1.5 New vaccination strategies

4.1.5.1 The Prikki study: development of an effective strategy for implementation of pertussis cocooning

Despite good coverage of childhood pertussis vaccination, infants under the age of six months remain a high-risk group for severe pertussis infection. Cocooning, i.e. vaccination of parents and healthcare workers (HCWs), has been recommended internationally as a method of reducing pertussis infection among this group. The Prikki study aimed to develop and test an effective strategy for the implementation of pertussis cocooning in the Netherlands, taking into account possible barriers and facilitators. Intention to accept pertussis vaccination and factors possibly associated with intention were studied among four target groups: maternity assistants, midwives, paediatric nurses and parents. Results showed that the intention differs among the target groups, varying from 41% to 78%. Important determinants of this intention are: cognitive attitude, direct perceived social norm and anticipated regret. Difficulties in decision-making also appeared to be a barrier to acceptance. Subsequently, an implementation strategy was designed that addresses these factors. Part of this strategy is an online decision tool that aims to enhance (ethical) reflection of the target groups on the subject. In 2014, the implementation strategy will be pilot tested. The results of this study will contribute to insight into the acceptance of pertussis cocooning in the Netherlands, which might be useful for policy making. Furthermore, the concepts found could be applicable in the context of other vaccinations.

4.1.5.2 Willingness among the elderly to receive vaccination

Over the coming years, the proportion of elderly people in the Netherlands will rise. As a result of immunosenescence (the gradual deterioration of the immune system), co-morbidity and general frailty, this population is more susceptible than younger people to infectious diseases. Vaccinating people over 50 years old against vaccine-preventable diseases (VPDs) may be one strategy for promoting healthy aging. Apart from possible benefits to individuals in this age group, vaccination may yield social benefits, such as lower overall costs of healthcare. To achieve high vaccination coverage, insights into the determinants of acceptance of vaccination are crucial. From focus groups, it was concluded that the elderly do not always consider themselves as vulnerable to infectious diseases because of their perception of good health. Nevertheless, vaccines against infectious diseases that cause illness, death, suffering or invalidity or affect their quality-of-life would be accepted in order for them to maintain independence. Side effects were not in themselves seen as a reason to decline vaccination. Finally, recommendations by the GP do not always influence the decision-making of the elderly.
In 2014, a discrete choice experiment will be performed to construct a generic model to estimate the willingness to accept vaccination against different VPDs among various age groups of elderly people (50 and older) and to determine the relative importance of the identified factors influencing their willingness to be vaccinated.

4.1.5.3 HPV vaccine acceptance by mothers and their daughters in a multi-ethnic cohort, Amsterdam

Ethnic groups that can benefit most from HPV vaccination unfortunately have lower acceptance and uptake of the HPV vaccine than the indigenous Dutch population. Research that provides estimates of HPV vaccine acceptance and uptake, and the factors associated with vaccine uptake, is needed for the design of effective public health interventions focused on decreasing disparity in uptake. A questionnaire to investigate HPV vaccine acceptance will be sent to all mothers and daughters with a Surinamese, Turkish, Moroccan, Ghanaian and native Dutch background at the beginning of February 2014. In addition actual vaccination behaviour will be obtained from the RVP registry. The intention to vaccinate will be linked to actual vaccination behaviour in order to assess the predictive power of intention. Results are expected in December 2014.

4.1.5.4 Vaccination coverage in anthroposophical CWCs

A first analysis based on existing data retrieved from the national vaccination register Præventis showed that vaccination coverage among children who have received at least one NIP vaccination through an anthroposophical CWC, which administer vaccines in the context of the NIP, is considerably lower than the average national coverage (Figure 1) [16]. Anthroposophical CWCs are visited not only by parents with anthroposophical beliefs but also by parents who prefer their approach and the longer duration of the consultations, and by parents who want to vaccinate according to an alternative vaccination schedule.
The largest difference in vaccination coverage was observed for the first MMR vaccination (45% versus 96% nationally, determined at two years of age). Data for vaccination coverage among children who visit an anthroposophical CWC are probably not accurate, because we do not know how many unvaccinated children visit such centres or an anthroposophical GP for the administration of vaccinations outside the NIP. It is important note that the number of children who received one or more NIP vaccinations in anthroposophical CWC is very small: it represents 0.3% or less of the total birth cohort. Furthermore, these children are probably as geographically clustered as the Reformed Orthodox group. Social clustering does occur at anthroposophical schools (vrije scholen). However, preliminary data from a regional study among some of these schools showed a self-reported vaccination coverage (=at least one vaccination) for DTaP-IPV of 91% (range 80–100%) and for MMR of 83% (range 45–100%).

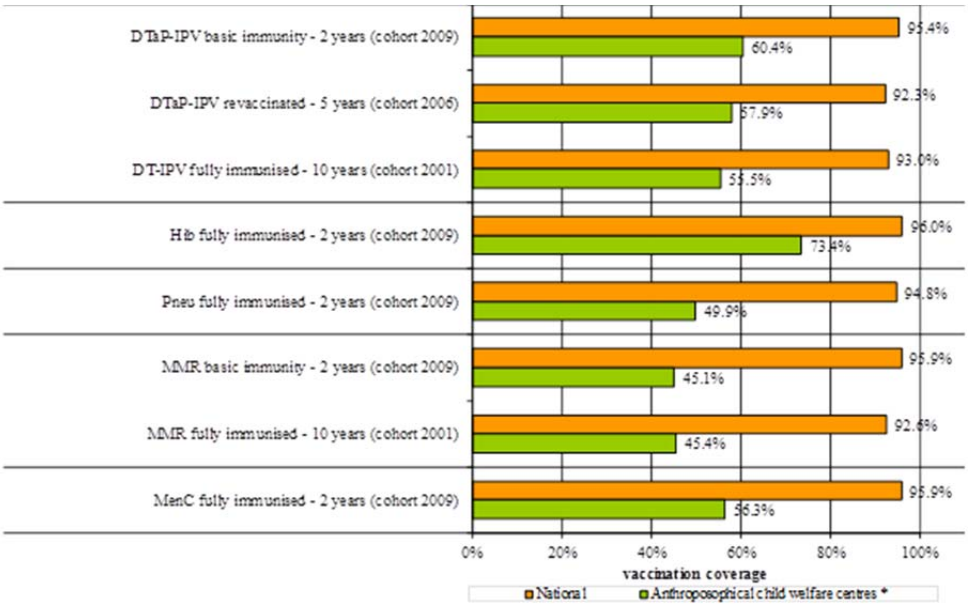


Figure 1 Vaccination coverage DT(aP)-IPV, Hib, Pneu, MMR and MenC: national versus anthroposophical child welfare centres
*All children who have received at least one NIP vaccination at such a centre (cohort 2009 n=561, cohort 2006 n=485 and cohort 2001 n=218)

The data also showed that the administration of the first DTaP-IPV vaccination is generally postponed among children who have received at least one NIP vaccination at an anthroposophical CWC (cohort 2010 n=315) (Figure 2). At national level, 85% of all administered DTaP-IPV-1 vaccinations in the first year of life were given on time (i.e. before the tenth week of life). Among children who had received at least one NIP vaccination through an anthroposophical CWC, this percentage was considerably lower (20%).

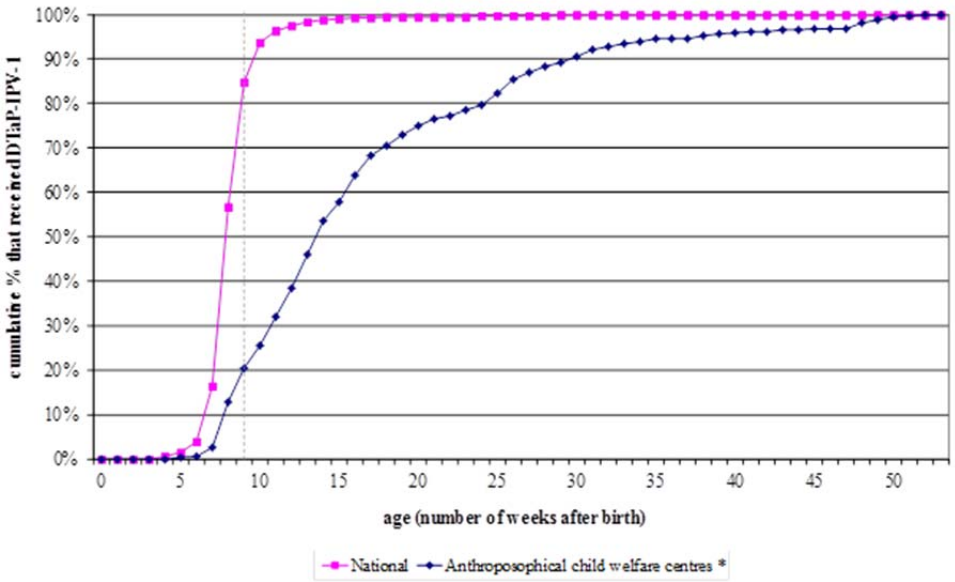


Figure 2 DTaP-IPV-1 vaccination by age (number of weeks after birth in the first year of life) at the moment of administration (birth cohort 2010), cumulative
*All children who have received at least one NIP vaccination in such a centre (cohort 2010 n=315)

4.2 Communication

The RIVM has a responsibility to communicate to professionals and the public about the NIP. The aim of communication about the NIP is to create public support and to enable parents and children to make a considered decision to vaccinate or not. Therefore, target groups (public, professionals, intermediaries and media) should have adequate knowledge and a good understanding of the NIP. In addition, anticipation of resistance to vaccination and the occurrence of hype, and the preparation of various risk scenarios belong to the communication task. Below, we describe some of the activities and materials for communications with professionals and the public.

In July 2013, a group of marketing en communications specialists, researchers and NIP professionals gathered to share ideas and insights on communications about the NIP. Some ideas where implemented immediately, others are useful in developing the communications strategy for the next few years.

4.2.1 Communication with professionals

Professionals often provide information on the NIP to parents. To support professionals, the RIVM produces a variety of communication materials: an NIP digital newsletter called 'Need to know', instructions for the administration of vaccines, a dossier with information on vaccination, FAQs, scientific reports, and brochures about religious and non-religious arguments against vaccination. These materials are also available from the 'professionals' section of the RIVM website, which is accessible by anyone. Once a year, a day for NIP professionals is organised where they receive information on the latest results and new developments within the NIP. Medical advisors from the RIVM have regular contact with professionals in their region about current events and new developments. Professionals can also ask questions of the RIVM by telephone or email.

4.2.2 Communication with parents

After the birth of a child, parents receive an information brochure together with an invitation letter for getting the first set of vaccinations. More information brochures are sent when the child turns 4 years, 9 years and (only for girls) 13 years old. All documents refer to the RIVM/NIP website, which provides extensive information about the NIP, including news reports, the vaccination schedule, information on each disease and vaccine within the NIP, FAQs, adio-visual information, and digital versions of all the invitation letters and brochures. Parents can also obtain information from their local CWC or youth health organisation (GGD). The RIVM has its own 'NIP' Facebook page, which those who are interested can follow or post questions and/or news items, and is active on Twitter, regularly posting tweets about the NIP. The Twitter account of the RIVM has more than 12,000 followers, mostly journalists and professionals. The RIVM also monitors the activity of social media with regard to the NIP, responds to social media comments when necessary, and invests in online advertising strategies (i.e. Google ranking), to make sure that parents find the RIVM website when searching for information on the internet.
At regional level, GGDs develop communication tools for their region. Almost all GGDs have information about vaccination on their websites, with links to the RIVM/NIP website. The RIVM now takes part in the developing process when possible, to ensure that regional communications products are in line with the national communications strategy en products.

In 2012, a four-year project started on interactive second-generation tailored education promoting the acceptability of HPV vaccination among mothers of invited girls.

5 Current National Immunisation Programme

5.1 Diphtheria

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

5.1.1 Key points

- In 2012, one case of diphtheria was reported in the Netherlands. In 2013 up to 15 September no diphtheria cases were reported.

5.1.2 Changes to the vaccine 2012–2013

In 2013, no changes to diphtheria containing vaccines used in the NIP were made. All infants continued to receive a primary series of hexavalent DTaP-IPV-Hib-HBV (Infanrix hexa; GSK). The booster dose at four years of age was DTaP-IPV (Infanrix; GSK) and at nine years of age DT-IPV (NVI).

5.1.3 Epidemiology

In 2012, one diphtheria notification was received. In 2013, up to 15 September, no diphtheria cases were reported.

5.1.4 Pathogen

From 3 September 2012 up to 15 September 2013, the RIVM received four *Corynebacterium diphtheriae* strains, all with the suspicion of cutaneous diphtheria. One patient had an unknown travelling history and the other three patients had visited Thailand, Indonesia and Malawi, respectively. All strains were tested as diphtheria-toxin-PCR negative strains.

5.1.5 Adverse events

The enhanced passive surveillance system, managed since January 2011 by Lareb, receives reports of adverse events following immunisation (AEFI) for all vaccines included in the NIP. In 2012, reports following infant doses of DTaP-IPV-Hib-HBV, scheduled at 2, 3, 4 and 11 months, amounted to 44% (n= 617) of the total number of reports (http://www.lareb.nl/Vaccins/Lareb-rapportages-en-publicaties). This number was somewhat higher than the number of reports in 2011 (n=557), but was within the range of numbers of reports in the period 2005–2010 (i.e. between n=593 and n=756).

For the fifth consecutive year, adverse events (AEs) after the DTaP-IPV booster vaccination at four years of age were the most frequent (n=423, 30%), mainly concerned local reactions with or without fever. Other studies have found that AEFI occurs mostly in young children and after the first vaccination [18]. However, in the countries concerned, the whole-cell pertussis vaccine was used in the primary series.

Combination vaccines offer protection against multiple diseases with fewer injections. In a randomised, open-label study, Tapiéro et al. showed that an investigational hexavalent combination vaccine administered at two, four, and six months of age concomitantly with PCV7 was well tolerated [19]. In a phase II study, an investigational heptavalent vaccine DTaP-IPV-HepB/Hib/MenC had a clinically acceptable safety profile when administered to infants and toddlers, although one infant experienced a serious adverse event (thrombocytopenia), which was considered to have been possibly related to vaccination [20]. The safety profile of a quadrivalent vaccine (DTwP/Hib; Quadrovax, Serum Institute

of India) administered as a booster dose was acceptable in children previously vaccinated with a pentavalent vaccine (DTwP-HepB/Hib; Pentavac, Serum Institute of India) [21].
The population-level safety benefits of the acellular pertussis vaccine may have been underestimated because only specific AEs were considered, not the overall impact on health services utilisation. Hawken et al. estimated that approximately 90 emergency room visits and 9 admissions per month were avoided by switching to the acellular pertussis vaccine, assessed in infants receiving four doses at 2, 4, 6 and 18 months of age [22].

5.1.6 Current/ongoing research

No specific diphtheria-related research is on-going. Routine surveillance is in place for signal detection. Currently, antibody concentrations against diphtheria in a large nationwide serosurvey, performed in 2006-2007, are ready for analysis [12, 23]. Results on seroprevalence and geometric mean titers (GMTs) are expected in 2014.

5.1.7 International developments

No relevant international developments occurred in 2012 and 2013.

5.2 Pertussis

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

5.2.1 Key points

- In 2012, a large pertussis epidemic occurred with the highest number of notified cases since the introduction of notifications in 1976.
- Data on GP consultations and hospitalisations from 2012 also showed an increase.
- In the first six months of 2013 the incidence of pertussis notifications was found to be low.
- *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 recommend possible additional preventive measures. The main focus of pertussis vaccination is to prevent severe pertussis in young, not yet fully vaccinated, infants.
- Pertussis outbreaks continue to be reported throughout the world.
- Maternal immunisation is recommended in several countries to better protect young, not yet fully vaccinated, infants.

5.2.2 Changes to the vaccine 2012–2013

No changes to the pertussis containing vaccines used were made during 2012. See section 5.1.2.

5.2.3 Epidemiology

5.2.3.1 Disease

In 2012, a large pertussis epidemic occurred, with the highest number of notified cases since the introduction of notifications in 1976. In contrast to previous years, the peak was observed in May. Following the large outbreak in 2012, numbers in the first half of 2013 were low, as expected (Figure 3).

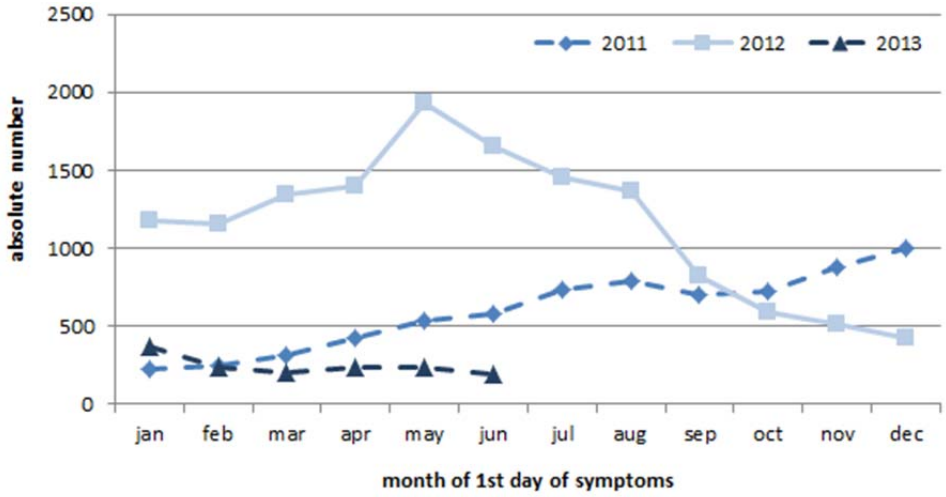


Figure 3 Number of notifications of pertussis per month for 2011, 2012 and 2013
Reports until 1 July 2013 are included.

Due to a delay between the day of onset of the disease and the day of notification, information for a calendar year is only complete in April of the following year. Age-specific incidence rates (IR) for the entire year 2012 show a similar picture as shown during the outbreak. Compared with other years with high disease rates, i.e. 2001, 2004, 2007 and 2008, infants up to two months old, children of eight years and older, adolescents and adults had high incidences in 2012 (Figure 4). In the first six months of 2013, all age categories had a lower incidence than in 2012. This is to be expected because the number of people susceptible to pertussis had decreased substantially due to natural infection.

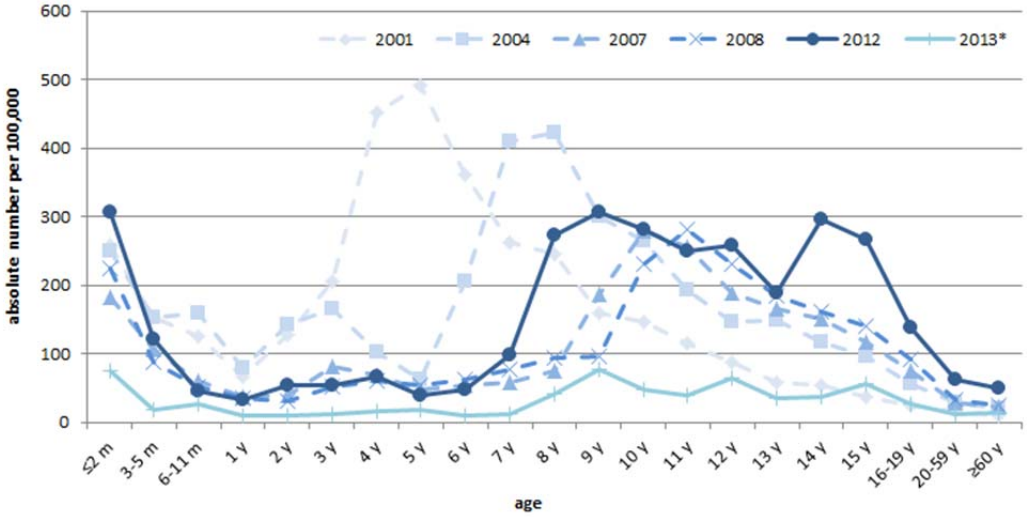


Figure 4 Age specific incidence of notifications per 100,000 for 2001, 2004, 2007, 2008, 2012 and 2013
*Reports until 1 July 2013 included.

All age-specific incidences of GP patients with pertussis showed an increase in 2012, except for 1–4–year–old children (Figure 5). The increase was most prominent in children under one year old and in adolescents aged 10–14 years.

The incidences in previous years shows fluctuations similar to those seen in the 2012 notifications. However, the peak in 2000 is not visible in the notifications and from 2005 onwards peaks are less prominent, compared to the peaks in notifications.

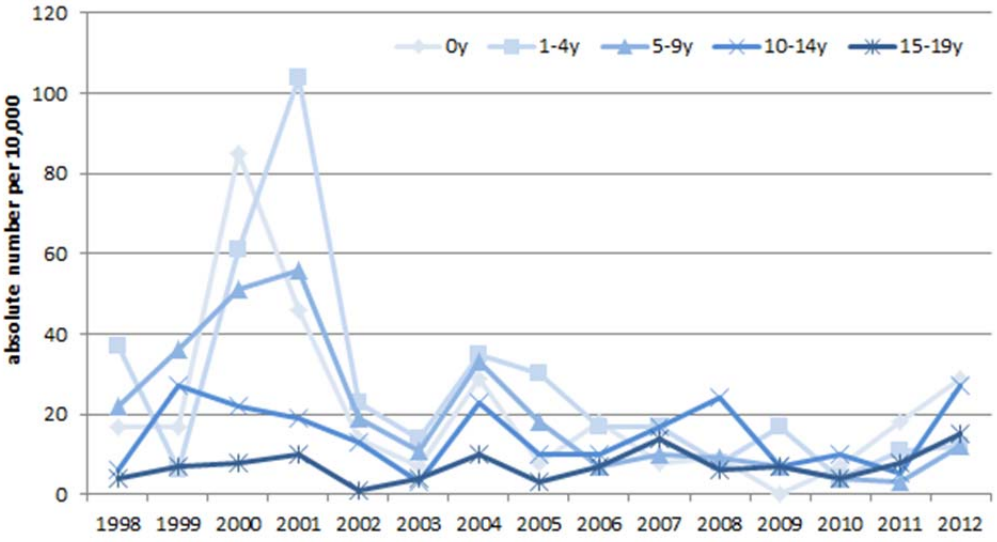


Figure 5 Age-specific incidence of GP patients with pertussis per 10,000 for 1998–2012

Likewise, an increase was visible in pertussis-related hospitalisations in 2012, most prominent in infants under two months of age (Figure 6A and Figure 6B). Although hospitalisations in older children, adolescents and adults were low compared with those in infants, the incidence among 10–15- and over 15-year-olds increased from 0.3 and 0.07 per 100,000 in 2011 to 0.9 and 0.29 per 100,000 in 2012, respectively.

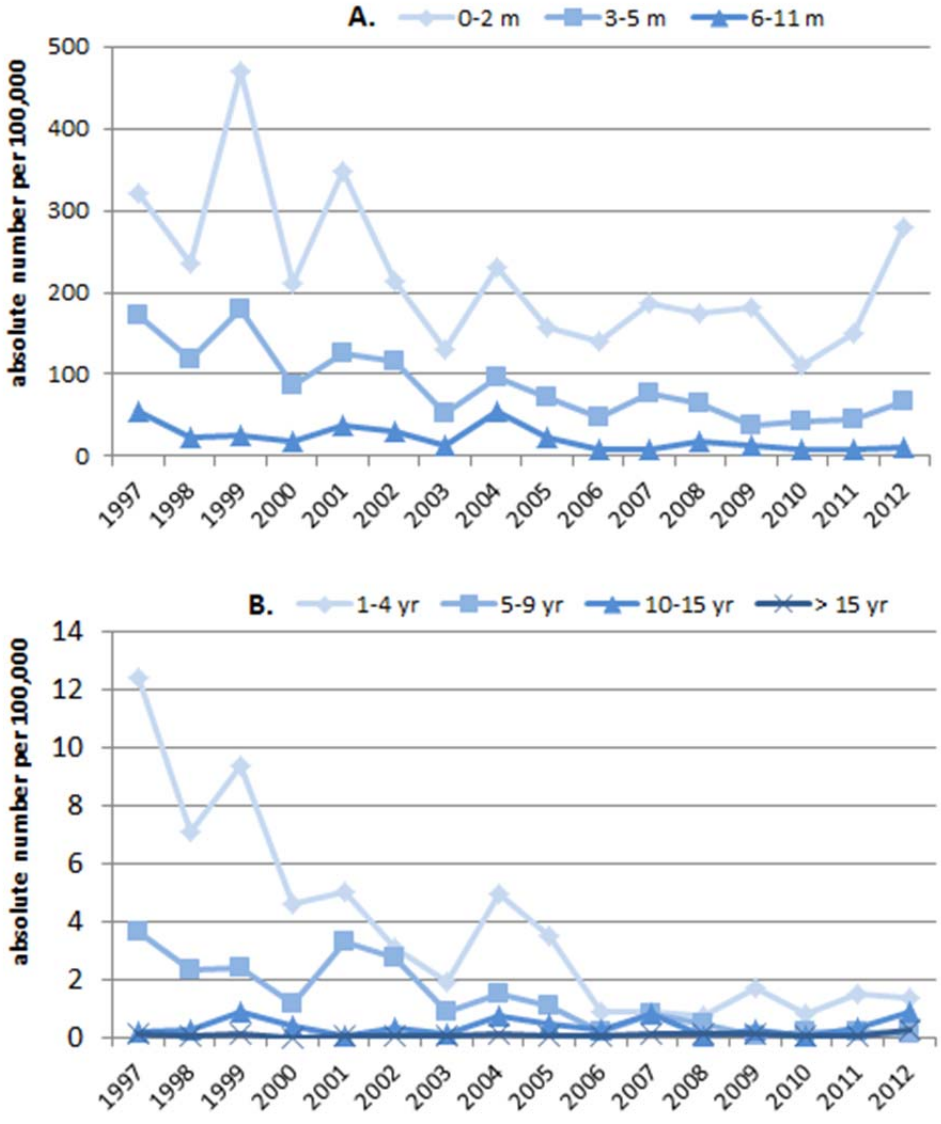


Figure 6 Incidence rates per 100,000 for hospitalisations in 1997–2012 of A. 0–2-, 3–5 and 6–11-month-olds and B. 1–4-, 5–9-, 10–15 and >15-year-olds

In 2011, two people (an 85-year-old man and a new-born infant) died of pertussis. In 2012, a one-month-old twin died in January, followed by an 87-year-old female in November 2012. In February 2013, a 6-week-old girl died due to pertussis.

5.2.3.2 Vaccine effectiveness

Table 4 shows vaccine effectiveness (VE) according to the screening method for the infant vaccination series. 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 estimation. 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 the 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 4 Estimation of vaccine effectiveness of the primary series of infant vaccinations by the 'screening method' for 1-3-year-olds per year[a]

Age	'94	'95	'96	'97	'98	'99	'00	'01	'02	'03	'04	'05	'06	'07	'08	'09	'10	'11	'12
1yr	77	92	32	29	38	63	78	73	63	29	54	72	87	92	90	90	97	97	97
2yr	58	42	63	-	33	22	52	46	41	-	-	67	58	92	91	89	93	91	93
3yr	79	60	38	-	9	-	-	-	54	10	37	59	43	84	82	83	89	88	87

[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 5).

Table 5 Estimation of vaccine effectiveness of the preschool booster by the 'screening method' for 5–14-year-olds per birth cohort

Birth-cohort/age	5yr	6yr	7yr	8yr	9yr	10yr	11yr	12yr	13yr	14yr
1998		74	68	77	73	60	-	45	-	18
1999	77	70	71	75	63	-	11	3	-	
2000	71	80	68	56	36	13	-	14		
2001	82	79	71	47	49	24	5			
2002	86	71	51	35	34	59				
2003	80	61	61	72	69					
2004	84	89	67	80						
2005	83	87	86							
2006	93	90								
2007	89									

For some age groups, the proportion of vaccinated cases exceeded the vaccine coverage of the population (92%). Therefore, VE could not be estimated. This short duration of protection of an acellular pertussis booster has also been observed in several other countries [24, 25]. Furthermore, analysis of pertussis data for birth cohorts according to whether they received exclusively acellular pertussis vaccines, exclusively whole-cell pertussis vaccines or mixed schedules showed that children primed with whole-cell vaccine had lower pertussis rates than children, who had received only acellular pertussis vaccinations in their first year of life [26].

5.2.3.3 Cost-effectiveness

Rozenbaum et al. evaluated the cost-effectiveness of several extended pertussis booster vaccination strategies in the Netherlands [27]. He developed an age structured dynamic transmission model to evaluate the impact of programmes targeting (i) adolescents or adults using a single booster dose, (ii) a combination of adolescent and adult vaccination, and (iii) a decennial booster dose. The base case analysis, that is a single adolescent booster administered at the age of 12 years, resulted in a reduction in pertussis infections. However, the benefits in terms of quality adjusted life years (QALYs) gained and costs saved in children were partly offset by an increase in the number of symptomatic infections in adults. Despite these negative indirect effects in the adult population, administering an additional booster dose could still be considered cost-effective, with an incremental cost–effectiveness ratio (ICER) of € 4,200 per QALY gained, according to this analysis. Combining an adolescent booster dose at the age of ten (most cost-effective age for a single adolescent booster dose) with an adult

(18–30 years) booster dose always resulted in favourable ICERs (<€ 10,000/QALY). Finally, the decennial booster dose resulted in an ICER of € 16,900 per QALY. Rozenbaum et al. concluded that extended pertussis booster vaccination strategies are likely to be considered as cost-effective. In another publication Rozenbaum stated that, in general, adolescent vaccination was found to be cost-effective but not highly effective in protecting infants too young to be vaccinated [28]. The US Advisory Committee on Immunization Practices (ACIP) recommends pregnancy vaccination as a preferred and safe alternative to postpartum vaccination. Terranella compared the cost-effectiveness of the acellular pertussis vaccination during pregnancy with postpartum vaccination with or without vaccination of other close contacts (i.e. cocooning) [29]. She concluded that pregnancy vaccination could reduce annual infant pertussis incidence by more than postpartum vaccination, reducing cases by 33% versus 20%, hospitalisations by 38% versus 19%, and deaths by 49% versus 16%. Acellular pertussis vaccination during pregnancy could avert more infant cases and deaths at lower cost than postpartum vaccination, even when postpartum vaccination was combined with additional cocooning doses. Thus, they concluded that pregnancy dose vaccination is the preferred alternative to postpartum vaccination for preventing infant pertussis. Ding performed a cost–benefit analysis of hospital-based postpartum vaccination with combined tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine [30]. If including direct medical costs only, the strategy would not generate net savings from a healthcare system perspective. However, from a societal perspective, this strategy is likely to generate net benefits.
Meregaglia assessed the number needed to vaccinate (NNV) to prevent hospital admissions in infants (<12 months) and the potential cost-effectiveness of a parent-cocooning strategy in Piemonte, Italy [31]. The NNV for parental immunisation was at least 5,000 to prevent one infant hospitalisation in the latest epidemic cycle (2005-2010) at a cost of >€ 100,000. The 'cocoon' programme led to net costs from a National Health Service perspective (returns on investment <1). In contexts of low incidence and without reliable data on a high parent-attributable infant risk, the parental 'cocoon' programme is inefficient.

5.2.4 Pathogen

In 2012, 85 *Bordetella pertussis* strains isolated from patients suspected of having contracted pertussis were received, whereas in 2013 the number was only seven, in line with the large outbreak in 2012 and the low number of notifications in 2013. All seven strains carried the *ptxP3* pertussis toxin promoter variant. The *ptxP3* strains were found at a frequency of 92% (range 64% to 100%) from 2004 to 2012. In a previous study, we have shown that *ptxP3* strains produce more pertussis toxin than the *ptxP1* strains they have replaced [32]. More recently, we have found that in addition to pertussis toxin, *ptxP3* strains also show enhanced expression of genes involved in resistance to complement and reactive oxygen species [33]. We presume that these strains are 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 the adaptive immune system. Like *ptxP1* strains, *ptxP3* strains show (small) differences in the amino acid sequences of pertussis toxin and pertactin compared with the pertussis vaccine strains [32]. Consistent with the trend observed in the last five years, serotype 3 strains were found in higher frequencies in 2013 than in 2012 (respectively, 43% and 18%). We presume that these changes were 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. Pertactin-deficient strains have been identified in recent years in France (14%), Japan (26%), Finland (8%) and the US (92%) [34-37]. Before 2010, pertactin-deficient strains were not detected in the Netherlands. In 2010, 2011 and 2012, the percentage of Pertactin-deficient strains was 4%, 5% and 0%, respectively. In 2013, this percentage increased to 14%. In view of the low number of isolates, this increase should be interpreted with caution.

5.2.5 Adverse events

See section 5.1.5.

5.2.6 Current/ongoing research

The case control study, set up by the CIb and the Netherlands Pharmacovigilance Centre 'Lareb', to assess differences in cellular immune responses after the fifth dose of acellular pertussis at four years of age between children with an extensive local reaction and children without such a local reaction has finished inclusion [38]. Results are expected in 2014.

As described in the report by Conyn et al., maternal immunisation is an alternative measure for the protection of very young infants [39].
Within the CIb a study proposal for a maternal vaccination trial has been approved by the Central Committee on research involving human subjects (CCMO). The main objective of this trial is to compare anti-pertussis toxin antibody concentrations in infants at three months of age (i) born to mothers vaccinated against pertussis during the third trimester of pregnancy and (ii) born to mothers vaccinated directly after birth in order to determine wether active transport of maternal–specific pertussis antibodies induced by maternal vaccination can protect the infant in the first months of life. In both groups, infants will receive the first DTaP-IPV-Hib-HepB vaccination at three months of age. Furthermore, all fathers will be vaccinated against pertussis also, to diminish the risk of the infant contracting pertussis as much as possible. The recruitment of participants is ongoing.

5.2.7 International developments

The increase in pertussis observed in 2012 in the Netherlands also occurred in many other, developed countries, including the UK and US [40, 41]. The Joint Committee on Vaccination and Immunisation (JCVI) for England and Wales is studying the effects of different interventions, including a booster dose in teenagers and the vaccination of pregnant women, healthcare workers and neonates, or close contacts of neonates. Recently, the UK 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, aimed at decreasing the disease burden in very young infants. In the US, the Advisory Committee on Immunisation Practices (ACIP) has updated recommendations for the use of acellular pertussis vaccine (Tdap) in pregnant women and people who have close contact with an infant aged <12 months [42].
In both countries, the first infant vaccination is scheduled at two months of age. Likewise, the maternal immunisation trials currently being performed in the US and Canada have a first infant dose at two months of age. Results are expected in 2014. The results of the Dutch maternal vaccination trial, described under 5.2.6, will provide additional information on the anti-pertussis toxin antibody level at three months of age without infant vaccination.

At the 10th International Congress on Bordetella in Dublin this year, scientists argued that the acellular vaccine indeed protects children in their first years of life but that (pre)adolescent and adult boosters have only limited effectiveness. Participants stated that the current acellular vaccines need to be adapted or replaced by new vaccines that provide longer immunity.

5.3 Tetanus

N.A.T. van der Maas, H.E. de Melker, R. Donken, D.W. Notermans, J.M. Kemmeren, S.J.M. Hahné

5.3.1 Key points

- In 2012, two cases of tetanus were reported; one case was vaccinated, the other had an unknown vaccination status.
- In 2013 (up to 5 September), no cases of tetanus were reported.
- Low numbers of cases of tetanus are reported almost every year, mostly among the elderly. Some of these cases visited a physician and did not receive tetanus post-exposure prophylaxis, indicating that Dutch Health Council recommendations on tetanus post-exposure prophylaxis are not always followed properly.
- In the Netherlands, only 28% of the guidelines health care workers use for tetanus post–exposure prophylaxis are consistent with the recommendations of the Dutch Health Council, published in 2003. In the remaining 72% of the guidelines used, there is a increased risk of over-prescription and/or under-prescription.

5.3.2 Changes to the vaccine 2012–2013

In 2012 and 2013, no changes to the tetanus toxoid-containing vaccines used in the NIP were implemented. See section 5.1.2 for details.

5.3.3 Epidemiology

In 2012, two cases of tetanus were notified. The first case was a 21-year-old male who had suffered a dog bite. He received all vaccinations except for the booster dose at nine years of age. The second case was a 70-year-old male with a wound. His vaccination status was unknown. He did not contact a physician and did not receive post-exposure prophylaxis. In 2013 (up to 5 September), no cases of tetanus were reported.

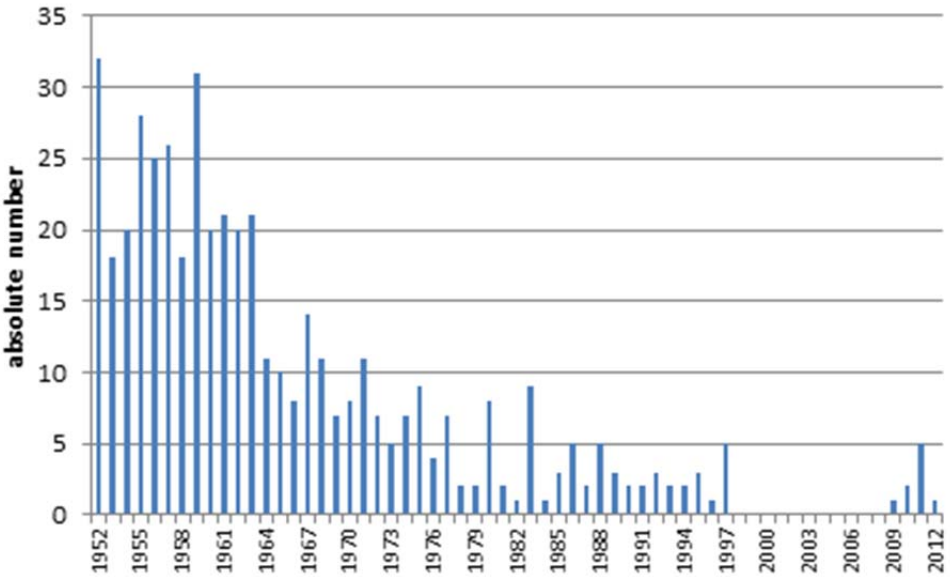


Figure 7 Reported cases of tetanus in the Netherlands by year, 1952-2012.
Note: Between 1999 and 2009 tetanus was not notifiable.

5.3.4 Pathogen

Clostridium tetani was not isolated from the reported cases in 2012, which is usual for tetanus.

5.3.5 Adverse events

See section 5.1.5.

5.3.6 Current/ongoing research

Low numbers of cases of tetanus are reported almost every year in the Netherlands. Some of these cases have visited a physician and not received tetanus post-exposure prophylaxis. This suggests that the Health Council (HC) recommendations on tetanus post-exposure prophylaxis (T-PEP) are not always followed properly [43]. These recommendations were reviewed in 2003. The RIVM-CIb studied whether the HC recommendations on T-PEP were in place, using a questionnaire survey among GPs and emergency departments (EDs). Ninety-eight per cent of the respondents reported using guidelines on T-PEP. However, only 28% was consistent with the HC recommendations. For EDs this percentage was 41%; for GPs it was only 21%. Furthermore, 36% of the respondents used guidelines that were consistent with the guidelines of the Dutch College of GPs. The latter guidelines are more restrictive, because they also take into account whether a wound is tetanus-prone.
The remaining 36% of participants used other guidelines, whichin 10% of cases led to over-prescription of T-PEP in fully vaccinated individuals. Over-prescription of T-PEP increases the risk of side effects and causes unnecessary costs. Furthermore, for specific risk groups, information on T-PEP was missing, perhaps indicating a risk of under-immunisation (Donken et al., manuscript in preparation). Under-immunisation puts people at risk for contracting tetanus. To improve adherence to guidelines the use of a bedside test, i.e. the Tetanus Quick Stick, to establish the patients' immune status quick, should be considered, for instance in certain risk groups.
The RIVM-CIb study on the usefulness of the Tetanus Quick Stick in three Dutch EDs is ongoing. Results are expected in 2014.

5.3.7 International developments

No relevant international developments occurred in 2012 and 2013.

5.4 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

5.4.1 Key points

- In 2012 and 2013 (as at 1 November) no cases of poliomyelitis were reported in the Netherlands, in spite 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.
- In Israel, wild poliovirus type 1 (WPV1) has been detected in 91 sewage samples, indicating country wide transmission. No cases of paralytic polio have yet been identified. Travel to Israel by unvaccinated persons is strongly discouraged. Travel organisations are actively informed of vaccination recommendations for travellers to Israel.
- Cases of poliomyelitis have been confirmed in Syria, where almost all infrastructure for public health and medical services has been destroyed during the continuing civil war.
- The influx of Syrian refugees to the Netherlands and the number of Dutch people visiting religious sites in Israel, give cause for assessing the risk of reintroduction of polio in the Netherlands.
- No wild poliovirus type 3 was detected globally by acute flaccid paralysis (AFP) or environmental surveillance in 2013. The last virus reported was an AFP case in Nigeria in November 2012.
- The WHO has launched a Polio Eradication and Endgame Strategic Plan 2015–2018.

5.4.2 Changes to the vaccine 2012–2013

No changes to the vaccines containing inactivated poliomyelitis virus (IPV) used in the NIP were made during 2013. See section 5.1.2.

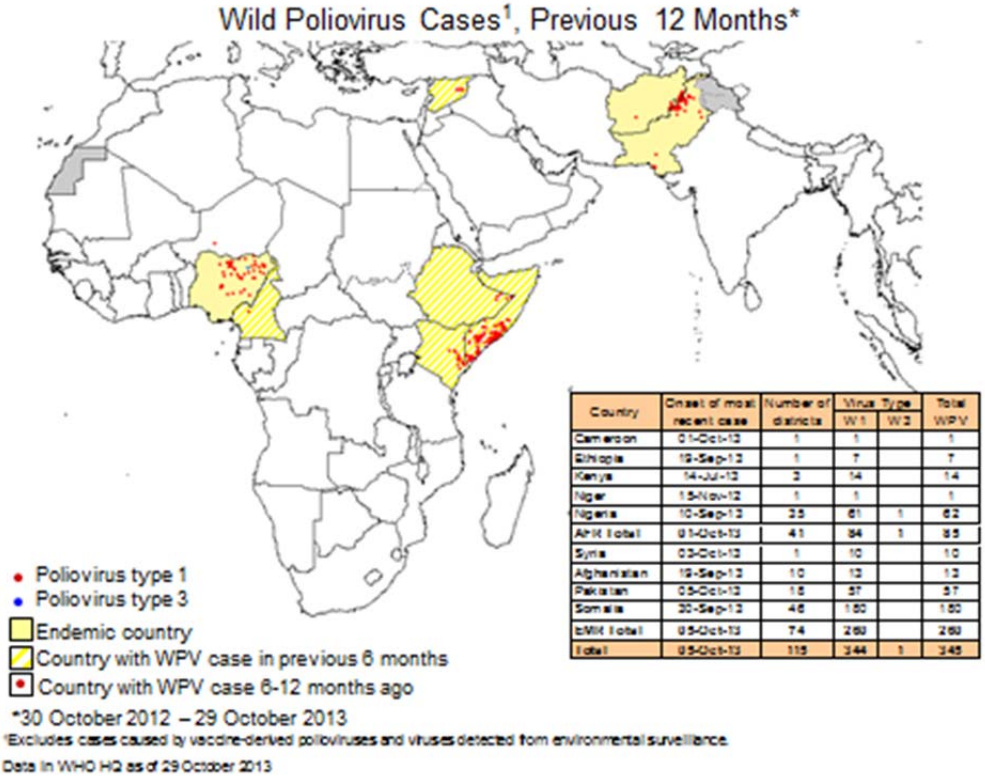
5.4.3 Epidemiology

5.4.3.1 Polio eradication initiative: global situation in 2013

No wild poliovirus type 3 has been detected in the world by acute flaccid paralysis (AFP) or environmental surveillance since November 2012. The last AFP case caused by wild type 3 virus was found in northern Nigeria.
In 2013, polio remained endemic in three countries – 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 notified suffered the onset of paralysis on 19 September (WPV1), bringing the total to eight cases in 2013.
In Pakistan, WPV transmission is also restricted to three groups of districts. The total number of cases in 2013 (until September) was 53, the most recent case of WPV1 being on 5 October. In addition, Pakistan and neighbouring Afghanistan repeatedly re-infect one other, due to the substantial population movements between and within the two countries.
Vaccination campaigns in northern Pakistan were greatly hampered and sometimes even stopped locally as vaccination staff are at risk of being killed or kidnapped by anti-government factions.

Nigeria is one of the most entrenched reservoirs of wild poliovirus in the world, with ongoing transmission of WPV1. The vaccine-derived poliovirus (VDPV) type 2 epidemic that was active for several years in Nigeria seems to have come to an end in 2013. The total number of cases reported in 2013 up to the end of October was 49. 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 the progress needed to finish the job.

Until poliovirus transmission is interrupted in these countries, all countries remain at risk of importing polio. Depending on the level of immunity in the population and the country's proximity or travel ties to polio-endemic countries, outbreaks can result from these importations. A number of countries continue to be affected by such outbreaks. Most of these are in the 'wild poliovirus importation belt' – a band of countries stretching between West Africa to central Africa and the Horn of Africa. The most recent example was the large outbreak in Somalia with up to 200 cases, due to severe political unrest that stopped all vaccination efforts. The virus causing the outbreak originated from Pakistan and it has since been exported from Somalia to neighbouring Kenya, Ethiopia and South Sudan.
In 2013, for the first time in history, the number of polio cases in non-endemic countries exceeded the number of cases in the three endemic countries, which have never been free of polio.
Environmental surveillance has shown extended and continuous circulation of wild poliovirus type 1 in Israel without cases of paralytic polio, since February 2013. Wildtype poliovirus type 1 environmental samples have also been detected on the West Bank (two sites) and in the Gaza strip (one site). Since 2005, only inactivated polio vaccine (IPV) has been used for routine childhood immunisation in Israel. To interrupt WPV1 transmission, nationwide supplementary immunisation activity (SIA) with bivalent oral polio vaccine (OPV) targeting children under ten years of age has been ongoing since August. The first effect on the number of positive sampling sites and the levels of excreted wild type poliovirus are observed. Unvaccinated people are discouraged from travelling to Israel via targeted information. Travel organisations are regularly updated on the specific situation in Israel.
In October 2013, cases of wild type poliovirus causing poliomyelitis were reported in Syria, where the continuing civil war has disrupted all medical and public health infrastructure.
Vaccination campaigns in refugee camps in neighbouring countries started immediately, even before confirmation of the cases in Syria.



Country	Onset of most recent case	Number of districts	Virus Type		Total WPV
			WT	WD	
Cameroon	01-Oct-13	1	1		1
Ethiopia	19-Sep-13	1	7		7
Kenya	14-Jul-13	2	14		14
Niger	15-Nov-12	1	1		1
Nigeria	10-Sep-13	35	61	1	62
AFR Total	01-Oct-13	41	84	1	85
Syria	03-Oct-13	1	10		10
Afghanistan	19-Sep-13	10	13		13
Pakistan	05-Oct-13	15	37		37
Somalia	30-Sep-13	46	150		150
EMR Total	05-Oct-13	74	260		260
Total	05-Oct-13	115	344	1	345

Figure 8 Wild poliovirus cases worldwide, 2012-2013

5.4.4 Pathogen

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 people. For poliovirus type 1 and 3, suspected VDPVs have ten or more nucleotide changes in the VP1 gene compared with the corresponding Sabin strains; for poliovirus type 2 the number of differences must be at least six.

These viruses can cause outbreaks of poliomyelitis, indistinguishable from wild-type epidemics Suspected VDPVs are classified as i-VDPVs, when linked to an immune-deficient person; as circulating or c-VDPVs when associated with two or more cases of acute flaccid paralysis; and as ambiguous or a-VDPVs in all other cases (for instance when isolated from sewage). The withdrawal of the polio 2 component of OPV as part of the Endgame strategy (see above) will prevent the emergence of new type 2 c-VDPVs, the most frequently observed serotype to develop to VDPVs.

Table 6 Circulating vaccine-derived Poliovirus, 2000-2013 (WHO, data in WHO/HQ as of 3 September 2013)

Country	**cVDPV type 1**														**Most recent**
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	**case**
Mozambique												2			2 June '11
Myanmar							1	4							6 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**
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	**case**
Cameroon														3	19 July '13
Pakistan													16	12	13 July '13
Nigeria						3	22	71	66	154	27	34	8	1	6 June '13
Yemen												9			5 Oct '11
Somalia									1	6	1	9	1	1	9 Jan '13
Afghanistan											5	1	9	3	13 March '13
Kenya													3		29 Aug '12
Chad											1		12	4	12 May '13
DR Congo									13	5	18	11	17		4 Apr '12
China													2		6 Feb '12
Niger							2			2	1	1		1	11 July '13
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**
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	**case**
Yemen													2		24 Aug '12
Ethiopia										1	6				4 Nov '10
Cambodia						1	1								15 Jan '06

5.4.5 Adverse events

See section 5.1.5.

5.4.6 International developments

The WHO has launched the Polio Eradication and Endgame Strategic Plan 2015-2018, with four objectives:
1. detection and interruption of all poliovirus circulation
2. strengthening immunisation systems and withdrawing OPV (starting with OPV2)
3. containment of poliovirus and certification of interruption of transmission
4. planning of the legacy of polio

The Polio Eradication and Endgame Strategic Plan 2015-2018 addresses the eradication of all polio disease, whether caused by wild poliovirus or by circulating vaccine-derived poliovirus, while planning for the backbone of the

polio effort to be used to deliver other health services to the world's most vulnerable children. Upon a resolution of the World Health Assembly, expected in early 2015, that wild poliovirus circulation has been interrupted, the use of OPV2 will be banned and global use of tIPV will ensure immunity to poliovirus type 2 (and of course the other two types). The withdrawal of the polio 2 component in OPV as part of the Endgame strategy (see above) will prevent the emergence of new type 2 cVDPVs, the most frequently observed serotype to develop to VDPVs. In this Endgame strategy, even after polio eradication, continued immunisation against poliomyelitis is foreseen to prevent the risk of a global outbreak due to accidental or deliberate re-introduction of the virus. After the planned OPV withdrawal, IPV will be the vaccine of choice for polio vaccination. However, this could result in vaccine shortage, and IPV is considered an expensive option for low income countries. Therefore, the WHO called for new polio vaccines [44, 45]. In response, following the demonstration of a proof of principle in the 1990s [46], Intravacc (formerly part of the RIVM and the Netherlands Vaccine Institute), continued the development of a Sabin-IPV (an inactivated poliovirus vaccine based on attenuated 'Sabin' polio virus strains).
Development of Sabin-IPV plays an important role in the WHO polio eradication strategy as bio-containment will be critical in the post-OPV cessation period. The use of attenuated Sabin strains instead of wild-type Salk polio strains will provide additional safety during vaccine production. Initially, the Sabin-IPV production process was based on a scaled-down model of the current, and well-established, Salk-IPV process [47]. In parallel with clinical trial material production, process development, optimisation and formulation research is being carried out to further optimise the process and reduce cost per dose [48, 49]. Master- and working virus seedlots (for technology transfer purposes), and clinical trial material (for phase I studies) have been produced on an industrial scale under current Good Manufacturing Practice (cGMP) conditions [50]. Safety and preliminary immunogenicity in adults were demonstrated for the use of this Sabin-IPV vaccine in 2011 [51, 52]. Next, a comparable study in adults was performed in Cuba. Based on the promising results of this study, a phase I/IIa clinical trial assessing safety and immunogenicity in infants (the target population) in Poland was recently finished. Results of the trial indicated that the vaccine can be considered safe and immunogenic against poliovirus infection.
It is planned to transfer the developed technology to local vaccine manufacturers in low- and middle–income countries [50]. The transfer of technology at the first individual manufacturer site (Panacea, India) was started in 2012. In collaboration with the WHO, five other potential partners, from South Korea, China (x2), Mexico and India, were selected. Future partners will receive the existing Sabin-IPV production process and related quality control (QC) testing procedures and will be encouraged to participate in optimisation of the process in order to make the vaccine more affordable.

5.5 *Haemophilus influenzae* serotype b (Hib) disease

L. Mollema, M.J. Knol, P. Kaaijk, N.Y. Rots, J.M. Kemmeren, H.E. de Melker, A. van der Ende, G.A.M. Berbers, L. Spanjaard

5.5.1 Key points

- There were no significant changes in the number of invasive disease cases caused by *Haemophilus influenzae* serotype b (Hib) in 2012 and 2013 (up to July) in the Netherlands.
- A stable number of vaccine failure of invasive Hib disease is seen during the last years.

5.5.2 Changes to the vaccine 2012–2013

There have been no changes to the vaccine containing *Haemophilus influenzae* serotype b (Hib) used in the NIP. In 2012 and 2013, all infants were offered hexavalent DTaP-IPV-Hib-HBV vaccine (Infanrix hexa; GSK) at 2, 3, 4 and 11 months of age.

5.5.3 Epidemiology

5.5.3.1 Disease

After the introduction of vaccination in 1993, the number of cases of Hib disease decreased from 246 in 1993 to 12 in 1999. However, in 2002-2005 the number of cases of Hib disease increased again, with a peak of 49 cases in 2004. Since then, the annual number of cases has decreased again to an average of 27 cases. In 2012 and 2013 (until July), the number of cases amounted to 28 and 11 respectively. After the introduction of vaccination in 1993, the number of cases caused by nontypable (unencapsulated) Hi strains (NTHi) increased from 30 in 1993 to 87 in 2003, partially because the number of blood isolates submitted for serotyping increased. From 2004 to 2009 the average number of cases was 78. Since 2010, the number of cases has increased to an average of 97 per year. This increase can be caused by the increased incidence among 0-4 year-olds and those aged 65 years and older. In 2012 and 2013 (until July), the numbers of NTHi cases were 100 and 56, respectively.

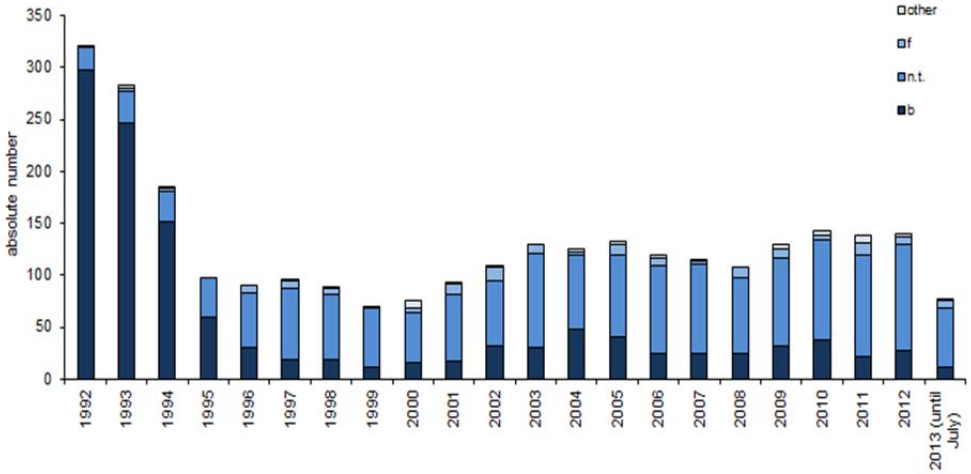


Figure 9 Absolute number of H. influenzae isolates by serotype, 1992–2013 (until July)

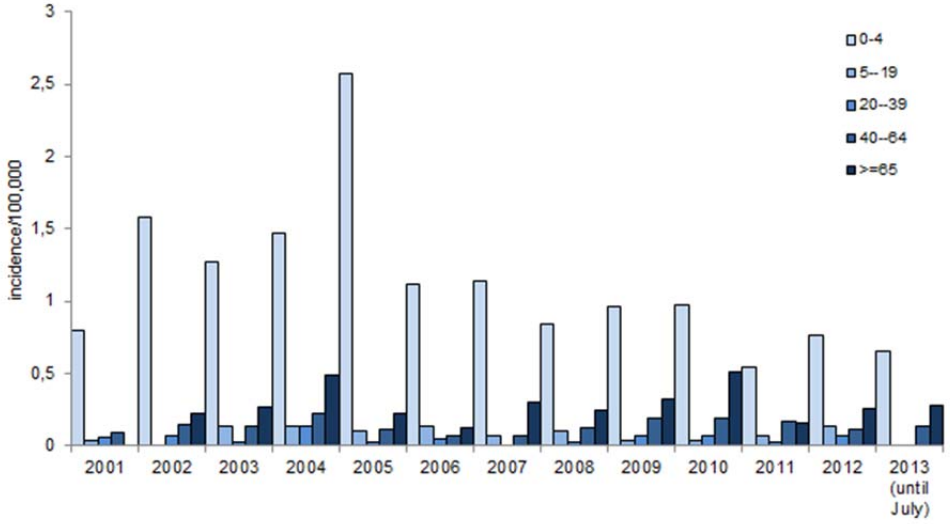


Figure 10 Age-specific incidence of patients with invasive Hib disease, 2001–2013 (until July)

5.5.3.2 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 decreased again in the following years. The number of true vaccine failures was 7 and 2 in 2012 and 2013 (until July), respectively.

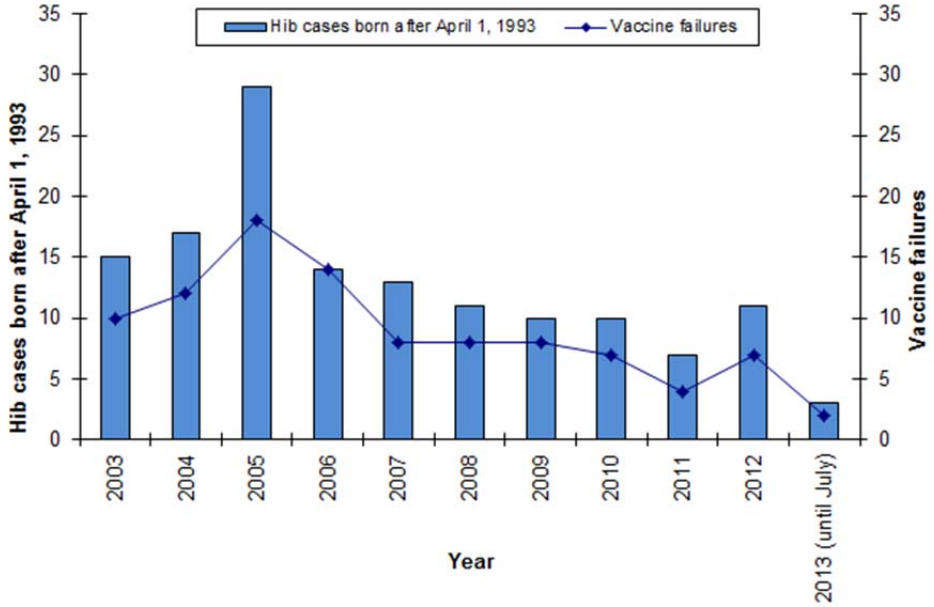


Figure 11 Annual number of Hib infections in people eligible for vaccination (i.e. born after 1 April 1993) and number of vaccine failures 2003-2013 (until July)

5.5.4 Pathogen

There are no indications that the pathogenicity of Hib has changed. Among NTHi isolates, the biotype II has been predominant during the last ten years [53].

5.5.5 Adverse events

See section 5.1.5.

5.5.6 Current/ongoing research

The prevalence of invasive Hib disease (IHD) and Hib vaccine failure was studied in the period 2003-2012. The following definition of true vaccine failure was used: 'invasive Hib disease occurring any time after receipt of 3 doses of Hib conjugate vaccine given in the first year of life, >1 week after receipt of 2 doses given in the first year, or >2 weeks after receipt of a single dose given after the first year'. In the period 2003-2012 there were 100 cases of true vaccine failures out of 142 (70%) cases eligible for vaccination according to their birth date. Most of the other 42 cases were not vaccinated (82%), received only one vaccination (2%), were too young to be vaccinated (2%) or had an unknown vaccination status (14%). The vaccine effectiveness was estimated at 88% (95% CI: 81-91%). Disease manifestation of vaccine failure cases was: meningitis (54%), epiglottitis (12%), sepsis (10%), pneumonia (10%) and other (4%). No increase in vaccine failures with IHD has been seen during the last years [54].

5.5.7 International developments

In four European countries (England, Finland, Poland, Germany) there has been an increase in the incidence of IHD caused by NTHi, mainly among elderly [55].

5.6 Mumps

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

5.6.1 Key points

- The mumps outbreak that started among students in late 2009 continued throughout 2010–2012 with clear seasonality, peaking in March each year. There was a shift in outbreak strains from G5 variant 1, the outbreak strain in 2010 to G5 variant 2, the strain which predominated in 2011 and 2012.
- In 2013, the mumps outbreak diminished, but there is still consistent reporting of mumps at rates higher than before 2010, indicating that there is still endemic transmission. This is consistent with the molecular detection of both G5 variants in most cases.
- During 2012–2013, with help of the ZonMW funded mumps research grant, several lines of research were initiated, which gave new insights into the possible causes of the outbreak in terms of mumps infectiousness, severity and immunological protection through vaccination.

5.6.2 Changes to the vaccine 2012–2013

No changes occurred in the MMR vaccine used in the NIP during 2012. The MMR vaccine was offered within the NIP to all children at 14 months and 9 years of age. During 2013, an MMR vaccination campaign for infants below 14 months of age was implemented as part of the measles outbreak response (see section 5.7).

5.6.3 Epidemiology

The genotype G mumps outbreak that started among students in late 2009 continued into 2010, 2011, 2012 and 2013 (Figure 12 and Figure 13). There was

clear seasonality, with an increase in the number of cases after the summer and a peak in March each year. The number of reported cases during the mumps season (September to August) was highest in 2010–2011 (689 notifications). The 2012–2013 season had the smallest number, with only 180 cases. Recent analyses suggest that this may be partly due to increased levels of immunity in the student population due to natural infection (J. Sane, manuscript submitted for publication). Transmission is continuing in 2013 but at low levels. Of all cases (September 2009 to August 2013, n=1737), 58.5% were male and the median age was 22 years (range 0–86 years). The age distribution and vaccination status of cases is shown in Figure 14. Of all the cases whose vaccination status was known (n=1,638), 67.5% were fully vaccinated (at least two doses of MMR), 10.4% had one dose of MMR and 17.6% were unvaccinated.
In total 36 cases were admitted to hospital; none died. For 143 cases (8.2%) a complication was reported (Table 7). Three cases of mumps-related permanent deafness were reported. Two of these were unvaccinated, and one was twice vaccinated. Two of the cases of deafness have been described in recent publications [56, 57].

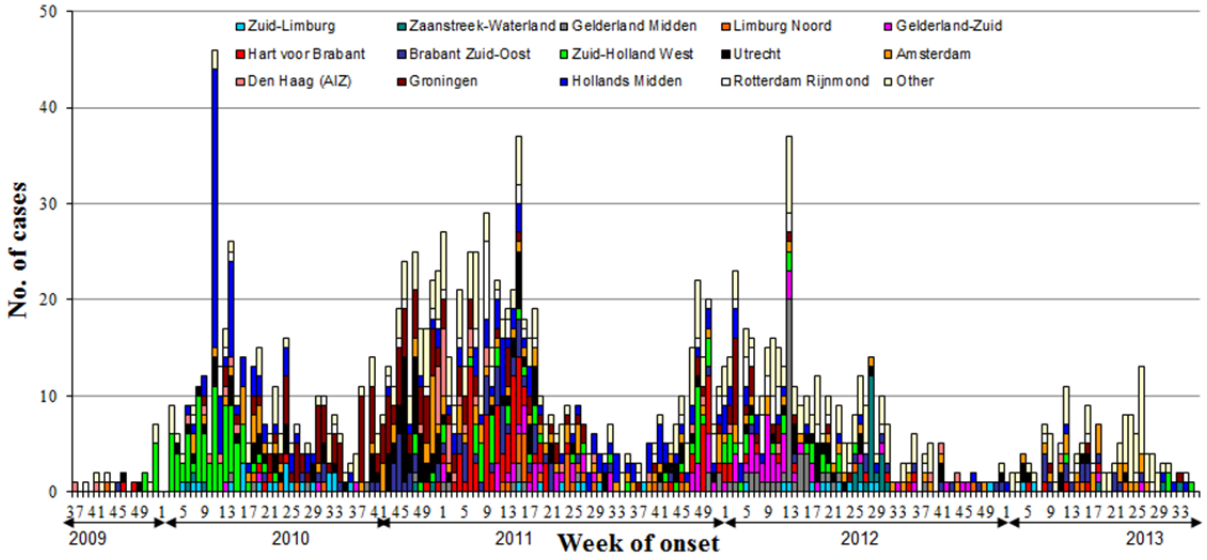


Figure 12 Number of notified mumps cases by week of onset and GGD, 01/09/2009 – 31/08/2013 (n=1737)

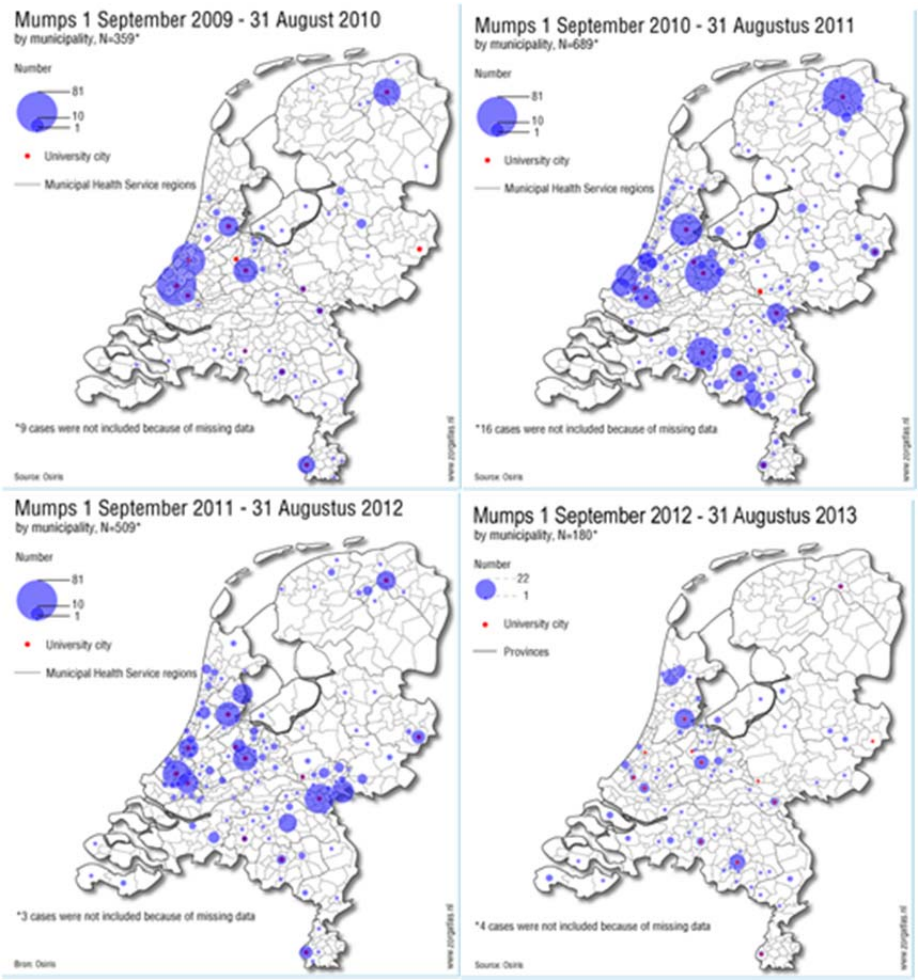


Figure 13 Number of notified mumps cases by municipality for four mumps seasons (September-August)

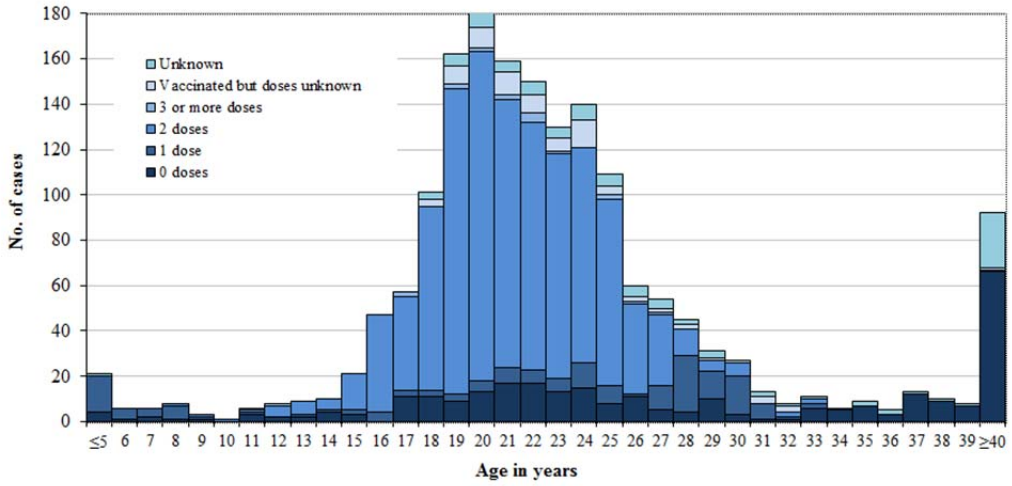


Figure 14 Number of notified mumps cases by age and vaccination status, 01/09/2009–31/08/2013 (n=1,737)

Table 7 Reported complications among cases of mumps notified between 01/09/2009 and 31/08/2013 (n=143)

Complications	**n**	**% of reported cases (n=1,737)**
Orchitis	121	11.9 (of men)
Meningitis	2	0.12
Orchitis & meningitis	4	0.4 (of men)
Encephalitis	0	0.00
Pancreatitis	2	0.12
Meningitis, encephalitis & pancreatitis	1	0.06
Thyreoiditis	1	0.06
Deafness	3	0.17
Other	9	0.52

5.6.4 Pathogen

Since the outbreak started in late 2009, there has been a shift in the predominance of outbreak strains. Whereas the first outbreak season was dominated by G5 variant 1 (MuVs/Delft.NLD/03.10), G5 variant 2 (MuVs/Scheemda.NLD/12.10) became the predominant mumps strain in 2011–2012. These strains seem to differ in their viral pathogenesis. The implications of this for transmission and severity are currently being investigated.

5.6.5 Adverse events

See section 5.7.5.

5.6.6 Current/ongoing research

The sero-epidemiological results from the PIENTER-2 study, which were discussed in the previous report, are now published [58].
In May 2011, ZonMW funded a mumps study, which incorporated the research objectives that had resulted from the Outbreak Management Team (OMT) meeting held on 31 January 2011. The objectives and preliminary results of the different work packages (WP) were:

WP1.1: to assess the attack rate of mumps and the proportion of cases that is symptomatic (serological study)
In this WP paired sera (prior to and after the mumps outbreak) were obtained from 822 students. The preliminary estimate of the overall attack rate is 6.4%, of which about a quater was symptomatic. Data on serological correlates for protection is pending.

WP1.2: to document transmission in a network of contacts of a mumps case in order to assess the relative infectiousness of asymptomatic mumps cases
In this WP, 11 networks were included with a total of 106 participants. Only one participant acquired mumps in the observation period (attack rate 2% (95% CI 0.1–10.3%)). This is a much lower attack rate than was found in outbreaks of mumps following parties [59], suggesting heterogeneity in transmission intensity.

WP1.3: to develop mathematical models to describe mumps virus transmission in student populations
Mathematical modelling carried out in the 1980s projected that mumps vaccine coverage of 75% would result in mumps outbreaks 30 years after the introduction of vaccination [60]. Work carried out in this work package demonstrated that the social contacts of students differ from those of non-

students in that the former relatively frequently meet with people in the same age group. Furthermore, it was demonstrated that waning immunity can have a similar effect to suboptimal vaccine coverage in causing outbreaks years after the start of the vaccination programme. The influx of new students each year is a contributing factor to mumps outbreaks.

WP1.4: to assess cellular immunological factors among mumps cases
This study involves the blood sampling of 23 laboratory-confirmed clinical cases and 21 non-infected controls. Laboratory investigation for serological and cellular profiling is ongoing.

WP2: to study the effects of mumps orchitis on fertility
So far 14 men with orchitis have been included in this work package. Preliminary results suggest a reversible decreased fertility after mumps orchitis.

WP3: to study the determinants of acceptance of vaccination among students
In the qualitative research nine students were included who had received a catch-up vaccination and 12 students who had not get a catch-up vaccination. While the determinants for vaccination acceptance did not differ between the two groups, their relative importance did. Only 1 of the 12 students who had not been vaccinated said they had heard of the catch-up campaign. The quantitative component of this WP studied 687 students. The perceived severity of the disease was the main determinant for vaccine acceptance. In total 39% of students were aware of the mumps outbreak and 8% reported to be aware of the catch-up campaign.

5.6.7 International developments

A recent paper describes an outbreak of mumps in a highly vaccinated Jewish population in New York. In this school-based study, an attack rate of clinical mumps of 13% was found. The only risk factor identified was an increasing number of mumps cases in the class [61]. This is consistent with findings in an overview paper regarding mumps outbreaks among Jewish populations in New York. The main conclusion of this paper was that intensity of exposure is the main determinant of vaccine failure [62].
In the same outbreak in New York County, the effectiveness of a third dose of MMR as post-exposure prophylaxis was studied. It was found that a third MMR dose administered as post-exposure prophylaxis (PEP) did not have a significant preventive effect on mumps [63].

5.7 Measles

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

5.7.1 Key points

- During 2012, ten measles cases were reported, eight of which had a documented origin of infection outside the Netherlands. The two remaining cases resulted in an indigenous measles incidence of 0.1/1,000,000, which is well below the WHO elimination target (1 per 1,000,000 population).
- In May 2013 an outbreak of measles started among the Reformed Orthodox population, which has low vaccine coverage. Up to 2 October 2013, 1,646 cases were reported. Due to the accumulation of susceptibles in the unvaccinated population since the previous measles outbreak in 1999/2000 reflected in seroprevalence results (PIENTER-2),

the current outbreak may exceed the previous one when over 3,200 cases were reported.

5.7.2 Changes to the vaccine 2012–2013

No changes occurred in the mumps, measles and rubella (MMR) vaccine used in the NIP during 2012–2013. The MMR vaccine was offered within the NIP to all children at 14 months and 9 years of age. During 2013, an MMR vaccination campaign for infants below 14 months of age was implemented as part of the measles outbreak response (see below).

5.7.3 Epidemiology

5.7.3.1 Measles cases in 2012

In 2012, ten measles cases were reported in Dutch citizens (0.6/1,000,000 population). Of the ten infections in Dutch citizens, eight cases were imported cases, while the remaining two cases acquired measles in the Netherlands (incidence of non-imported cases 0.1/1,000,000). This is well below the WHO target for elimination of 1/1,000,000 and a decrease compared with the 50 cases reported in 2011. Of the ten cases, seven (70%) were hospitalised. No deaths occurred. The age of the cases ranged between 0 and 48 years.
Of the ten cases, two were below the age of the first MMR (14 months). One was 14 months old and had been vaccinated two days before the date of onset. Wild-type measles virus was detected in this case. Of the remaining seven cases, two had been vaccinated with two doses and five were unvaccinated. Among the ten cases, two were epidemiologically linked.

5.7.3.2 Measles cases in 2013 (until 2nd October)

Early in 2013, several clusters of measles cases occurred that were linked to imported cases. In February/March 2013, the first cluster in the region of The Hague was related to a once-MMR-vaccinated GP, who had acquired the infection in Italy. Eight subsequent cases occurred, four of whom were healthcare workers (two colleagues of the GP and two healthcare workers taking care of an admitted measles case). The second cluster of four cases was reported by GGD Zuid-Holland Zuid in March, in unvaccinated children of the Orthodox Protestant denomination. This cluster did not spark a generalised measles outbreak within the orthodox community; its associated genotype differed from the one found in the subsequent bible-belt outbreak (see below). The third cluster comprised two cases in March: an airport employee and a relative. The fourth cluster of three cases was related to a case imported from India. The fifth cluster was in a twin related to an import from China. In addition, there were two isolated cases.

In May 2013, a large epidemic started among unvaccinated orthodox protestants, with initial cases mainly reported by GGD Zuid-Holland Zuid and GGD Rivierenland [64]. The source of infection of the index case is unknown. In this epidemic, 1,646 cases were reported up to 2 October 2013 (Figure 15). Of these, 95% were unvaccinated, and 59% were aged 4–12 years. Up to October 2nd, 104 cases were hospitalised, no deaths were reported. Based on the most recent national seroprevalence results, the outbreak is expected to continue, with a final size that may exceed that of the 1999/2000 outbreak [65].

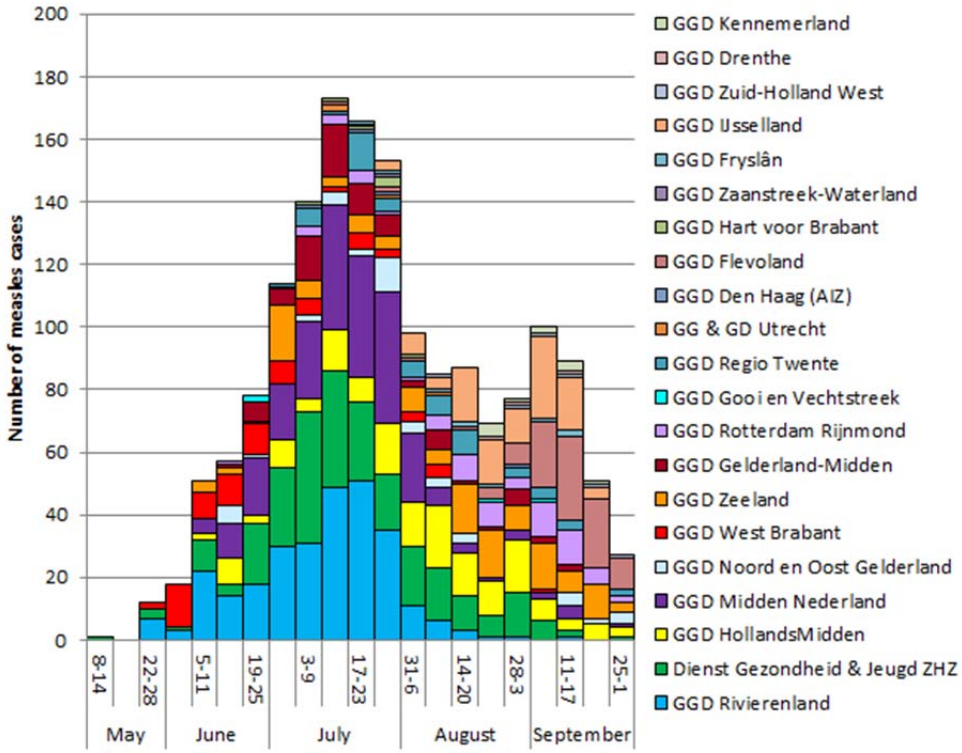


Figure 15 Reported measles cases by week of onset of hand rash, source: Municipal Health Service, (n=1,646), 1/5/2013 to 2/10/2013*
* Imported cases (n=26) are excluded here. An additional 33 cases are not included in the figure since information on the date of onset was missing

5.7.3.3 Outbreak response

Following advice by the Outbreak Management Team (meeting held 17/6/2013) and the Managerial Integration Meeting (*bestuurlijk afstemmings overleg* BAO; 19/6/2013) the Minister for Health and Welfare decided on the following interventions in response to the epidemic:

Early MMR vaccination for infants aged 6–14 months
Young infants are at higher risk of complications when infected with measles virus. Therefore, all infants between 6 and 14 months of age who are at increased risk of exposure to measles are offered additional protection. This protection consists of an additional MMR vaccination (MMR-0) for infants aged 6-12 months, and an early first MMR vaccination for infants aged 12-14 months. This intervention is offered during the epidemic to all infants in the 29 municipalities with MMR-1 vaccination coverage below 90%, and to all other infants in this age category whose parents are of the Orthodox Protestant denomination.

Catch-up vaccinations
Attention was raised to the possibility of free catch-up vaccinations within the NIP for all individuals up to 19 years of age who had not received two doses of MMR vaccine.

Outbreak response vaccination
In municipalities with vaccine coverage above 90% where measles outbreaks have occured, the GGD can decide on additional vaccinations for those who come into contact with infected cases.

Between May and August 2013, 5,376 infants below the age of one year received an additional MMR. In total 1,772 unvaccinated children above two years of age received their first MMR.

Protection of health care workers
Healthcare workers are at increased risk of contracting measles and of spreading it to vulnerable patients (e.g. immunocompromised patients). The RIVM therefore produced advice on how to protect healthcare workers against measles [66].
In a recent UK study, the cost-effectiveness of screening for immunity was compared with that of the MMR vaccination of healthcare workers using data from an occupational health service [67]. In the context studied, an estimated cost-saving of £ 105,000 per year could be achieved by offering vaccination without testing.

5.7.4 Pathogen

All measles cases genotyped in 2013 by the RIVM were of genotype D8. The different clusters and isolated cases listed above all had different subtypes, except the first measles cluster in 2013 in The Hague and the large epidemic among Orthodox Protestants, where indistinguishable genotypes were found, referred to as the 'Taunton' genotype, which currently (2013) has the highest prevalence in Europe. No epidemiological link was, however, detected between the cluster around The Hague and the Bible Belt outbreak.

5.7.5 Adverse events

In the Netherlands in 2012 the number of AEFI following MMR vaccination was 177 [68], compared with 233–315 in the period 2005–2010 and 156 in 2011. In most cases, MMR vaccination has been administered simultaneously with either MenC vaccination at 14 months of age or the dT-IPV booster at nine years of age. Based on the different risk periods for these vaccines, 45 reports could be ascribed to the MMR vaccine.
Two studies analysed reports of AEs related to MMR vaccine. The results of these studies showed that MMR vaccine is well tolerated with a constantly low rate of adverse events [69, 70]. A review of 32 years of clinical and post-marketing experience also provides evidence that the vaccine is safe and well tolerated [71]. In a study to examine the hypothesis that MMR exposure has a negative influence on cognitive development in children, no such relationship was found [72], and a review of vaccine administration and the development of immune thrombocytopenic purpura (ITP) in children showed that the incidence of ITP after MMR vaccination is significantly lower than that observed during the natural diseases that the vaccine prevents [73]. Consequently, ITP cannot be considered a problem limiting vaccine use except in the case of children suffering from chronic ITP who have to receive MMR vaccine. In these subjects, the risk-benefit ratio of the vaccine should be weighed against the risk of measles in the community.
A third dose of MMR vaccine administered in outbreak settings has been shown to be safe [74-76], with injection site reactions reported more frequently than systemic reactions [76]. However, to assess risk for rare or serious adverse events (SAEs) after a third dose of MMR vaccine, longer-term studies would be required.

5.7.6 Current/ongoing research

In response to the epidemic that started in May 2013, several lines of research were initiated by the RIVM-CIb in collaboration with other centres and municipal health services. These included the following :

1. Evaluation of the impact and effects of early MMR vaccination;
2. Assessment of serological correlates for protection;
3. Underreporting;
4. Validity of measles serology by different assays;
5. Implementation of advice for protection of health care workers;
6. Environmental surveillance of measles;
7. Transmission parameters of measles in social networks.

These studies are ongoing.

5.7.7 International developments

During 2012, the number of measles cases in the WHO European region decreased by over a third compared with 2011. Nevertheless, large outbreaks of measles were reported by the Ukraine (12,744 cases), Romania (4,271 cases), the Russian Federation (1,973 cases) and the United Kingdom (1,903 cases) [77].

5.8 Rubella

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

5.8.1 Key points

- The rubella incidence during 2012 was very low (1 case; 0.1/million population).
- In 2013, a large rubella outbreak occurred in Poland. Three cases with possible links to this outbreak were reported in the Netherlands in 2013, one of which could be partially genotyped (genotype 2B).
- During the first weeks of the measles epidemic in June 2013, a small and restricted rubella outbreak was identified at an orthodox school in the Hollands Midden region, where 54 related cases were reported. This was the largest rubella outbreak since 2004/2005.
- This rubella outbreak appeared to be caused by the same genotype 2B rubella virus as identified for the Polish rubella outbreak, but there are no epidemiological data to support a direct link. Genotype 2B is assumed to be the most prevalent in Europe on the basis of rubella reports in Europe in 2012.

5.8.2 Changes to the vaccine 2012–2013

No changes were made to the MMR vaccine used in the NIP during 2012. MMR vaccine was offered within the NIP to all children at 14 months and 9 years of age. During 2013, an MMR vaccination campaign for infants below 14 months of age was implemented as part of the measles outbreak response (see section 5.7).

5.8.3 Epidemiology

During 2012 one case of rubella was reported (incidence 0.1/million population). This was a 22-year-old female who was unvaccinated because of a critical attitude towards vaccination. In early 2013, three rubella cases were reported in young adults, of whom two were Polish and one had links with Polish people in the Netherlands. Subsequently, in June/July 2013, a rubella outbreak occurred at an Reformed Orthodox primary school in the Hollands Midden region. The first laboratory confirmed case occurred in the second week of June. In total 54 cases were reported, of which the last was reported within a family from another region (Midden Nederland) but was linked to the same school. The epidemiological curve of the outbreak is displayed in Figure 16. The median age

of cases was six years. Since 23 July 2013, no rubella cases linked to this school have been reported.

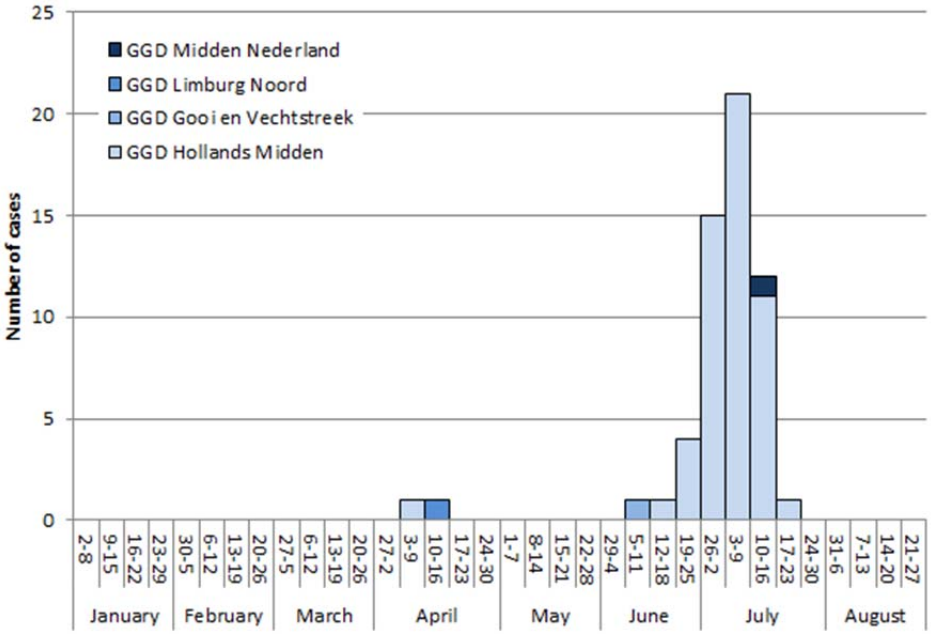


Figure 16 Rubella cases by week of onset and municipal health service (n=57), 1/1/2013 to 31/8/2013*
*Three cases are not included in the figure since information on their date of onset was lacking.

5.8.4 Pathogen

Sequence analysis is currently based on a 739 base pair (bp) window of the rubella virus E1 gene. In 2012, the RIVM laboratory adopted the two-step WHO/CDC rubella sequence PCR, which is directly applied to rubella PCR-positive clinical specimens. However, one particular rubella case in June, linked to an outbreak in Poland, could only partially be sequenced, because of low RNA concentrations detected in the clinical sample. The genotype could, however, be identified on the basis of a 525bp window, which was sufficient to identify it as genotype 2B rubella virus. The subsequent rubella outbreak, which started in June at an orthodox school, appeared to be caused by the same genotype 2B rubella virus as has been identified for the Polish rubella outbreak, but there are no epidemiological data to support a direct link. Genotype 2B is assumed to be the most prevalent genotype in Europe on the basis of rubella reports in Europe in 2012. For 2013, no data have yet been reported, except for the UK (according to the new WHO/HPA 'Rubens' genotype database).

5.8.5 Adverse events

See section 5.7.5.

5.8.6 Cost-effectiveness

Babigumira et al. performed a review of health economic evaluations of rubella and congenital rubella syndrome to assess the value of rubella vaccination, identify gaps in the evidence base and suggest possible areas of future research to support the planned global expansion of rubella vaccination and efforts towards rubella elimination and eradication [78]. Twenty-seven studies were identified, of which 20 has been conducted in high-income countries, 5 in upper-

middle income countries and 2 in lower-middle income countries. Congenital rubella syndrome was estimated to cost (in 2012 US$) between $ 4,200 and $ 57,000 per case annually in middle-income countries and up to $ 140,000 over a lifetime in high-income countries. Rubella vaccination programmes, including the vaccination of health workers, children, and women had favourable cost–effectiveness ratios in high- and middle-income countries. In order for research to support the global expansion of rubella vaccination and the drive towards rubella elimination and eradication, additional studies are required in low-income countries, to determine the most cost-effective programmatic strategies for increased rubella vaccine coverage.

5.8.7 Current/ongoing research

No rubella-specific research projects are currently ongoing within the RIVM.

5.8.8 International developments

In 2011/2012, a large rubella outbreak occurred in Romania among unvaccinated adolescents [79]. Up to January 2012, 1,840 cases had been reported.
In Poland, a large rubella outbreak started in 2013 [80]. Up to April 2013, 21,283 cases had been reported, 81% of them among 15–29 year-old males. This reflects the history of immunisation in Poland (selective vaccination of adolescent girls since 1989, universal two-dose MMR vaccination since 2004). In the Netherlands, three cases occurred in 2013 that had a link to Poland (see sections 5.8.3 and 5.8.4). The rubella virus detected in the rubella outbreak at an orthodox reformed school in the Hollands Midden region in June/July 2013 was found to have the same sequence as one of the imported cases from Poland. There was no epidemiological link, however, between this imported case and the outbreak.

5.9 Meningococcal serogroup C disease

L. Mollema, M.J. Knol, P. Kaaijk, N.Y. Rots, J.M. Kemmeren, A.W.M. Suijkerbuijk, H.E. de Melker, A. van der Ende, G.A.M. Berbers

5.9.1 Key points

- The incidence of meningococcal serogroup C (MenC) disease has greatly decreased since the introduction of vaccination in 2002.
- An immunogenicity study among children vaccinated against MenC during the catch-up campaign showed that nine years after vaccination 45% of 15-year olds had protective antibody levels, 34% of 12-year olds and only 19% of 10-year olds.
- No increase in MenC cases has been observed so far, but the need for a MenC booster in adolescents might be taken into consideration regarding the observed waning antibody titers against MenC.
- In June 2013, a MenC outbreak among men who have sex with men (MSM) was reported in Europe with a possible link to the outbreak in the US. No MenC cases among men older than 16 years were observed in the Netherlands. Since August 2013, the reporter of a case has been specifically asked to ascertain whether the case belongs to the MSM group.

5.9.2 Changes to the vaccine 2012–2013

There were no changes to the composition of the meningococcal serogroup C (MenC) vaccine or the vaccination schedule for MenC. MenC vaccine was offered to all children at 14 months of age.

5.9.3 Epidemiology

5.9.3.1 Disease

Since the introduction of the conjugated MenC vaccine in 2002 at 14 months of age with a catch-up for 1–18-year-olds, the incidence of Meningococcal serogroup C disease has greatly decreased (Figure 17). In 2012, only three cases of invasive meningococcal group C disease were reported: two new-borns and one 40 years old, all male. In 2013 (until July), four cases of MenC were reported, two unvaccinated females of 1 and 77 years old and two unvaccinated males, one from Poland of 28 years old and one from the Netherlands of 68 years old. The 77 year-old woman died. In 2013, individuals aged up to 29 or 30 years old were given the opportunity to be vaccinated with the conjugated MenC vaccine.

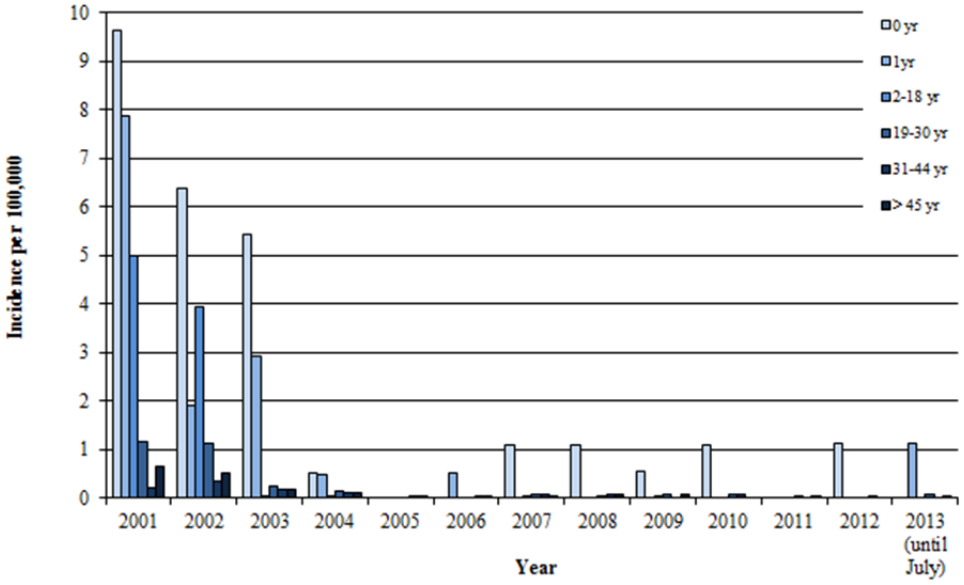


Figure 17 Age-specific incidence of meningococcal C disease (cerebrospinal fluid and blood isolates), 2001–2013 (until July)

Table 8 Absolute number of patients with meningococcal C disease, 2001-2013** (**Until July)*

Age in yrs	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013**
0 yr	20	13	11	1	0	0	2	2	1	2	0	1	0
1yr	16	4	6	1	0	1	0	0	0	0	0	0	1
2-18 yr	165	132	1	1	0	0	1	0	1	0	0	0	0
19-30 yr	29	28	6	3	0	0	2	1	2	2	1	0	1
31-44 yr	8	13	7	4	2	1	1	2	0	2	0	1	0
> 45 yr	39	32	11	7	2	2	3	6	5	0	2	0	1
Total	*277*	*222*	*42*	*17*	*4*	*4*	*9*	*11*	*9*	*6*	*3*	*2*	*3*

*Numbers may differ from the 2012 report as a different date variable was used.

Outbreak of meningococcal group C disease among men who have sex with men (MSM)
On 25 June 2013, Germany reported three cases of invasive meningococcal disease (IMD) among men who have sex with men (MSM) in Berlin, caused by *N. meningitides* serogroup C. Of the three HIV negative cases, two died. All three isolates were serogroup C, PorA-VR1: 5-1; PorA-VR2: 10-8 and FetA: 3-6 and confirmed as ST-11/ET-15. Retrospectively two more cases were identified, both closely related but one with a distinct variant. The age of the cases was between 23 and 28 years.
On 26 June, Belgium retrospectively reported a single case of IMD in a homosexual male diagnosed in March 2013; infection was due to a strain of the same sequence type as the German strain. The patient had reported travelling to London in the three weeks prior to onset of illness.
On 26 June, France reported three cases of IMD among MSM living in the Paris area. The three isolates were also of the same sequence type as the German and Belgian strains. Additionally, they reported two cases in July, one man and one woman. Retrospectively, they found 3 out of 63 MenC cases in males aged 16 years or older in the period 1 June 2010 to 31 December 2012 [81, 82].
Four similar outbreaks have been reported among MSM in Canada (Toronto, 2001 [83]) and the US (Chicago, 2003 [84]; Los Angeles, 2012 [85]; and New York City, 2010–2013 [85]). The outbreak in Toronto involved six cases aged 23–39 years of which two died. The outbreak in Chicago involved six cases aged 27–42 years of which three died. The outbreak in Los Angeles involved four cases with no further details known. The outbreak in New York City involved 22 cases, mean age 34 years; 12 cases were HIV-positive and 7 died.
Why does this infection affect the MSM population? A possible explanation might be higher carriage: epidemiological studies in MSM have found high carriage of oropharyngeal *N. meningtidis* (43%) and 2% rectal and 1% urethral colonisation rates [86]. Furthermore, it is unclear whether HIV is an independent risk factor for meningococcal disease.

Between the European cluster and the clusters in the US and Canada no epidemiological link could be found. Further microbiological studies are needed to provide laboratory evidence of direct and indirect transmission between the European cases mutually, as well as between the European and US cases. Most isolates of the NY outbreak were indistinguishable by pulsed-field gel electrophoresis and the outbreak strain was related to a serogroup C outbreak that occurred in 2006 among Brooklyn drug users and their close contacts.
In response to the outbreaks, public health authorities tried to increase awareness in the MSM community and among healthcare workers, and provided chemoprophylaxis and MenC vaccinations for identified contacts. The recommendations by the ECDC [81] included that Member States should consider retrospective investigations of cases of serogroup C IMD in young men in order to identify similar cases in the past should try to raise awareness among MSM and should consider vaccination as a means of outbreak control.

In the Netherlands, we are not aware of any MenC cases among MSM with the same subtype as in the 'Germany cluster'. Since August this year, the reporter of a case has been specifically asked to ascertain whether the case belongs to the MSM group. Since 2010, this specific subtype has only been demonstrated once: in 2013 in a girl too young to be vaccinated. Before 2010, the subtype was demonstrated five times in men older than 16 years in the period 2004–2009. In June, the Outbreak Management Team gathered to discuss the situation for the Netherlands and to formulate recommendations with experts from different fields. It was concluded that, based on the current situation in the Netherlands,

there was no justification for a general vaccination campaign. MSM who were vaccinated during the vaccination campaign in 2002 were well protected. MSM older than 30 years who wanted to travel to cities where local MSM communities were advised to receive a vaccination (e.g. Berlin, Paris and New York) and had the intention to have intensive contacts with various partners, were advised to consider vaccination before travelling. This advice will be continued as long as the above-mentioned local advice remains in force.

5.9.3.2 Vaccine effectiveness

Since the introduction of conjugate MenC vaccine in 2002, three vaccine failures have been reported. Two cases had an immunodeficiency. In 2012 and 2013 (until July), no vaccine failures were reported.

5.9.4 Pathogen

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

5.9.5 Adverse events

In the Netherlands in 2012, the number of AEFI following MenC vaccination was 103 [68]. However, most MenC vaccinations were administered simultaneously with MMR vaccinations at 14 months. Based on the different risk periods for these vaccines, only four reports could be ascribed to the MenC vaccine.

Four tetravalent Meningococcal vaccines are currently available; one with the 4 polysaccharide (PS) conjugated to TT (Nimenrix, GSK), one with the 4 PS conjugated to CRM (Menveo, Novortis), one with the 4 PS conjugated to D (Menactra, Sanofi Pasteur), and a meningococcal ACWY polysaccharide vaccine Mencevax ACWY, GSK).
Meningococcal quadrivalent vaccines have shown a good safety profile in infants when given in a one-dose or two-dose schedule [87], in children who have previously received two doses of meningococcal vaccine and in those who were previously meningococcal vaccine naïve [88]. MenACWY-D was also safe when given in two doses to infants and toddlers even in combination with other childhood vaccines [89]. However, in an investigational heptavalent combination vaccine (DTaP-HBV-IPV-Hib-MenC-TT), one infant experienced a SAE (thrombocytopenia), which was considered possibly related to vaccination [20]. Furthermore, in children aged 2–10 years MenACWY-TT had a clinically acceptable safety profile when compared with MenACWY-CRM [90] or MenACWY-PS [91], although a higher incidence of local reactogenicity with MenACWY-TT was observed [92].
Several trials assessed the safety of MenACWY-TT and MenACWY-CRM over a longer period. All studies showed that both vaccines had a clinically acceptable safety profile after three or five years [91, 93-96].

In adults, MenACWY-TT was also well tolerated compared with MenACWY-PS [97, 98]. Two subjects reported SAEs with MenACWY-TT containing 92% O-acetylation, of which one was considered related to vaccination (blighted ovum) [98].

5.9.6 Cost-effectiveness

Hepkema et al. [99] evaluated the cost-effectiveness of meningococcal vaccination at 14 months and an additional vaccination at the age of 12 years, both with a recently licensed MenACWY vaccine. A decision analysis cohort model, with 185,000 Dutch new-borns, was used to evaluate the cost-

effectiveness of different immunisation strategies. Vaccination with MenACWY at 14 months proved to be cost-saving. With the current epidemiology, a booster dose with MenACWY is not cost-effective. When immunity has waned, resulting in an increase of MenC cases, a booster dose has the potential to be cost-effective.

5.9.7 Current/ongoing research

When extrapolating the MenC PS-specific IgG and seroprevalence results of the PIENTER-2 study to 2013, individuals aged between 4 and 15 years might have excessively low protective antibody levels (serum bactericidal antibody (SBA) titers ≥8). Until now, no increase in MenC cases has been observed but the need for an MCC booster in adolescents might be considered. In October 2011, the TIM study started to establish the most appropriate age for a second MenC vaccination. Three groups of healthy 10-, 12- and 15-year-olds were recruited. All participants had received a primary MenC vaccination with the registered MenC vaccine (NeisVac-CTM, Baxter) nine years earlier, either at the age of 14 months (10-year olds) or during the mass catch-up campaign in 2002 (12- and 15 year olds). Nine years after primary MenC vaccination, 45% of the 15-year olds had protective antibody levels against MenC compared with 34% of the 12-year olds and 19% of the 10-year olds. All participants developed extremely high serum MenC-PS specific IgG levels and SBA titers one month after the study MenC vaccination. One year after the study vaccination, 100% of all age groups still had protective antibody levels against MenC (SBA titers ≥128). The 15-year-olds remained the highest serum MenC-PS specific IgG levels and SBA titers and showed the lowest level of decrease in antibody levels one year after the booster vaccination. More results are expected in 2014.

The clinical study to determine the carrier state of the various meningococcal serogroups among secondary school children and first year students is ongoing. The third and last sampling will be performed in autumn 2013.

Next year a second intervention study (JIM-study) will start to investigate the immune response to a tetravalent MenACYW-TT vaccine (Nimenrix, GSK) in 10-, 12- and 15-year-old children primed with the monovalent MenC-TT conjugate vaccine (NeisVac-CTM, Baxter) at a young age and to compare this response with the immune response after a monovalent MenC-TT conjugate booster vaccination.

5.9.8 International developments

In addition to the MSM outbreaks mentioned above, the vaccination schedule in the UK has been changed. A single dose at three months provides a good level of protection against group C meningococcal disease during the first year of life, which can then be maintained at 12–13 months with the Hib-MenC booster [100]. Therefore, babies in the UK will now receive just two doses of the MenC vaccine, one at three months and another at one year of age and no longer a dose at four months of age. From the 2013–2014 academic year teenagers in the UK will receive a booster dose of the vaccine. Carriage rates of MenC are known to increase during the teenage years, so vaccinating teenagers will have a significant impact on the level of herd immunity. Teenagers develop long-lasting protection following MenC vaccination, which will further increase the effectiveness of the new programme.
Many countries are now considering the need for a meningococcal C conjugate (MCC) booster in adolescents to counter the decline in antibody levels after initial and subsequent doses. Declining levels of immunity against MenC have been reported in Greece, the UK and Spain, as well as in the Netherlands [101].

Brazil has recently introduced routine vaccination with MCC vaccine, the first time that the vaccine has been used in a country in which most of the MenC isolates do not belong to the ST11 clonal complex. It will be important to follow the sero-epidemiological situation in this country to determine whether current experience with the MCC vaccine and the ST11 clonal complex can be extrapolated to other strains, considering the high rates of capsule expression of the strains belonging to the ST11 clonal complex [101].

The MenACYW-CRM vaccine (Menveo, Novartis) was already licensed for use in children (from two years of age), adolescents and adults and has now been licensed in the US for babies under two months of age. In Europe, the European Medicines Agency (EMA) did not consider the results of the clinical studies sufficient to support recommendation of the use of Menveo in children under the age of two years. First, it had not been shown that Menveo was at least as effective as the monovalent vaccine against *N. meningitidis* group C in this age group. Second, the clinical data showed a fall in antibodies between the third and fourth dose, which could result in children lacking protection between six months and one year of age.

5.10 Hepatitis B

S.J.M. Hahné, F.D.H. Koedijk, J.M. Kemmeren, N.Y. Rots, J. Cremer, A.W.M. Suijkerbuijk, A.J. King

5.10.1 Key points

- The incidence of acute HBV notifications, which had been decreasing since 2004, increased slightly in 2012 compared with 2011.
- Among men, sexual contact with men remained the most frequently reported risk factor.
- Molecular surveillance suggests that the ongoing transmission of the clonal genotype A strain, which has been detected since the start of molecular surveillance, continues.

5.10.2 Changes to the vaccine 2012–2013

Within the NIP hepatitis B virus (HBV), vaccination has been offered to all infants since 2011. Infanrix hexa (DTaP-Hib-IPV-HepB) is used at 2, 3, 4 and 11 months of age. No changes to the vaccine have occurred since its introduction in the NIP.

5.10.3 Epidemiology

In 2012, 1,513 cases of HBV infection were notified. Of these, 1,317 (87%) were chronic infections and 171 (11%) acute (25 cases were of unknown status). Compared with 2011, the number of notifications of acute HBV infection increased slightly (2011: 157 cases) [102]. The incidence of acute HBV notifications in 2012 was 1.0 per 100,000 population (2011: 0.9/100,000); 1.6/100,000 among men and 0.4/100,000 among women. The HBV incidence among men and women, which has been decreasing since 2004, seems to have stabilised in 2012 (Figure 18).

In 2012, most cases of acute HBV infection (64%) were acquired through sexual contact. For 29% of reports of acute HBV infection the most likely route of transmission remained unknown, despite source tracing. Among men (135 cases), sexual contact between MSM accounted for 30% of acute infections (n=41) and heterosexual transmission for 27%. Among women (35 cases), heterosexual contact accounted for 81% of cases.

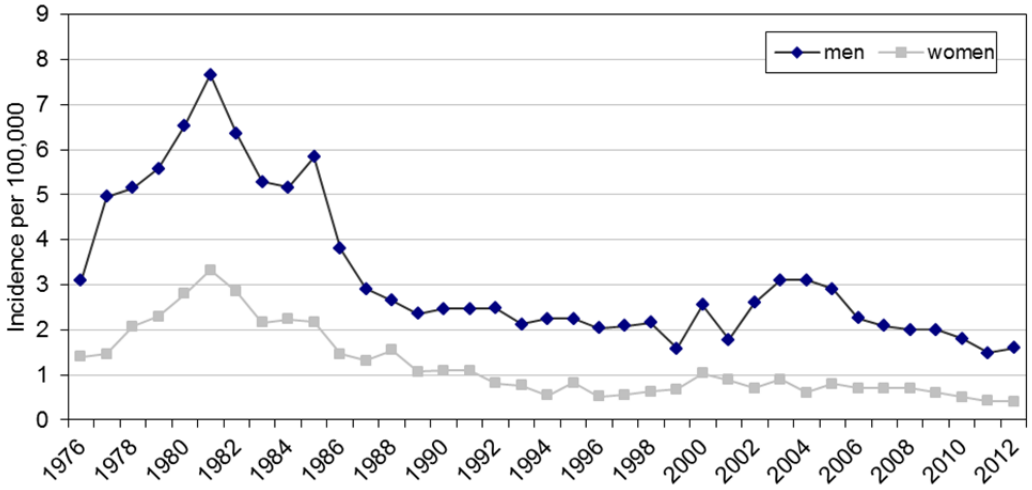


Figure 18 Incidence of notified acute HBV infections among men and women, the Netherlands, 1976–2012, Source: Osiris/IGZ database

Chronic HBV epidemiology
In 2012, most cases of chronic HBV infection (61%) were acquired through vertical trans-mission. Five percent were infected by sexual contact and for 24% of reports of chronic HBV infection the most likely route of transmission was unknown. Eighty-one percent of the chronic HBV patients were born abroad (with China, Turkey, Suriname and Ghana as most frequently reported counties of birth).

5.10.4 Pathogen

Molecular sequencing and typing of acute HBV cases continued in 2012. The RIVM received 89 samples for genotyping. PCR amplification and sequencing gave results for 86 (97%) samples for the S-region. A minimum spanning tree on the basis of S-region sequences is shown in Figure 19. This shows that the largest cluster of cases continues to be among genotype A cases.

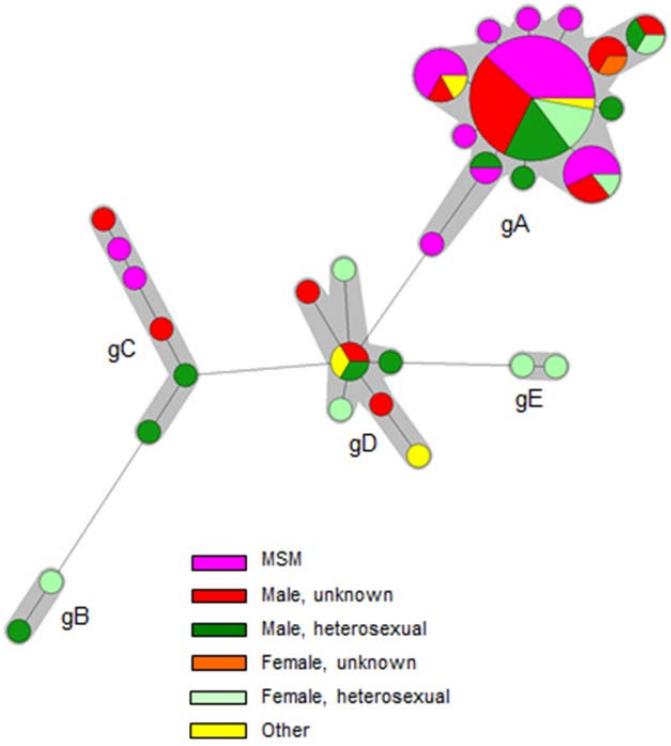


Figure 19 Minimum spanning tree based on the S-region sequence of acute HBV cases in 2012 by reported risk factor (n=86)

5.10.5 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 cannot be ascribed to the different vaccines. However, the number of reports received in 2012 is comparable to those in earlier years [68]. It therefore seems unlikely that the introduction of hepatitis B vaccination has led to more reports.
No safety issues were reported for licensed hepatitis B vaccines [103-107]. Furthermore, HBV vaccine (Shanvac, M/s Shantha Biotech) was demonstrated to be safe in patients with liver cirrhosis [108].
Several studies showed that the safety profile of the investigational hepatitis B surface antigen vaccine (HBsAg-1018) was comparable to that of the licensed vaccine HBsAg-Eng in healthy adults [109], as well as in patients with chronic kidney disease [110] and in non-responders to licensed hepatitis B vaccine [111].

5.10.6 Cost-effectiveness

Italy was one of the first countries in the world to introduce a routine vaccination programme against HBV for newborns and 12-year-old children in 1991. The objective of the study of Boccalini was to verify whether, 20 years after its implementation, hepatitis B universal vaccination had positive effects from an economic point of view [112]. She found that the implementation of vaccination had brought an extensive reduction in the burden of hepatitis B-related diseases in the Italian population. Therefore, the past and future savings due to medical costs avoided were high. The return on investment (ratio of benefit to costs) was nearly equal to 1 from the National Health Service perspective, and a benefit-to-

cost ratio (the net savings due to vaccination (in terms of disease treatment costs avoided plus indirect cost savings when the societal perspective is adopted) divided by the vaccination cost) slightly less than 1, considering only the first 20 years from the start of the programme. In a longer-time perspective, returns on investment and benefit-to-cost ratio values were positive (2.78 and 2.46, respectively). In conclusion, the implementation of universal hepatitis B vaccination was very favourable during the first 20 years of adoption, and further benefits are expected to be increasingly evident in the future.
Chen et al. compared the cost-effectiveness of HBV control strategies combining universal vaccination with hepatitis B immunoglobulin (HBIG) treatment for neonates of carrier mothers [113]. They developed a decision-analytic model to estimate the clinical and economic outcomes for four strategies: (i) universal vaccination; (ii) universal vaccination plus screening for hepatitis B surface antigen (HBsAg) and HBIG treatment for HBsAg-positive mothers' neonates; (iii) universal vaccination plus screening for hepatitis B e-antigen (HBeAg), HBIG for HBeAg-positive mothers' neonates; (iv) universal vaccination plus screening for HBsAg then HBeAg, HBIG for all HBeAg-positive, and some HBeAg-negative/HBsAg-positive mothers' neonates. Strategy 2 averted the most infections, followed by strategies 4, 3 and 1. In most cases, the more effective strategies were also more costly. In summary, the results suggest that maternal screening for HBsAg and HBIG treatment of neonates of HBV carrier mothers could be a cost-effective addition to universal vaccination. Particularly if the future treatment costs of HBV-infected children are expected to be moderately high, more intensive prevention efforts, using screening and HBIG, are likely to provide good value by averting those treatment costs.
A recent review of the prevalence of hepatitis B and C and the cost-effectiveness of screening concluded that hepatitis C virus (HCV) screening of people who inject drugs (PWID) and HBsAg screening of pregnant women and migrants are cost-effective [114]. In the Netherlands, HBsAg screening of pregnant women has been routinely offered since 1989. HCV screening of PWID is being implemented, and HBsAg screening of migrants is being considered.

5.10.7 Current/ongoing research

Molecular typing of notified acute HBV cases and of chronic HBV cases in the target groups for selective vaccination will continue in 2012 and 2013. Also ongoing is the participation of the RIVM-CIb in the EU project EUHepscreen (see section 5.10.8).
The decline in notifications of acute HBV among MSM was studied by mathematical modelling and phylogenetic analyses [115, 116]. Results indicate that the decline can mainly be attributed to the risk-group vaccination of MSM (implemented since 2002), which reaches the most at risk within this group, i.e. those MSM with many different sexual partners. The recent slight increase in the number of cases of acute HBV requires further study.

5.10.8 International developments

The EU-funded project EUHepscreen started at the end of 2011 and continues up to the end of 2014. 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 led by the GGD Rotterdam/Erasmus MC and includes 12 European partner institutions, including the RIVM. Further details can be found on www.hepscreen.eu. The project aims to deliver relevant information for the Netherlands should migrant screening for HBV/HCV be implemented. Over the past years several local HBV/HCV screening projects for migrants have been implemented in the Netherlands, some of which have been published [117,

118]. However, national policy on this is not yet available [119]. In September 2013, the ministry of health requested advice on migrant screening for HBV and HCV from the health council.

5.11 Pneumococcal disease

M.J. Knol, H.E. de Melker, P. Kaaijk, N.Y. Rots, J.M. Kemmeren, A.W.M. Suijkerbuijk, A. van der Ende, K.E.M. Elberse, G.A.M. Berbers

5.11.1 Key points

- The introduction of vaccination against pneumococcal disease to the NIP (in April 2006) has led to a considerable reduction in the number of cases of invasive pneumococcal disease (IPD) caused by the serotypes included in the 7-valent pneumococcal conjugated vaccine (PCV7) in all age groups.
- The reduction in IPD caused by PCV7 serotypes has been partly counterbalanced by an increase in non-PCV7 serotype IPD. The overall incidence decreased for 0–4-year-olds and adults over 65 years of age but remained more or less stable in other age groups.
- A decrease of IPD caused by the three additional serotypes included in PCV10 (implemented in May 2011 in the NIP) was seen among 0–1-year-old children.
- An immunogenicity study (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 schedules. Importantly, after the booster dose at 12 months, all four immunisation schedules showed similar and protective antibody concentrations, showing that a reduced schedule could be considered.
- The PIEN study comparing PCV10 and PCV13 showed that antibody levels were generally higher for PCV10 before the booster dose and higher for PCV13 after the booster dose.

5.11.2 Changes to the vaccine 2012–2013

Children born after 1 March 2011 in the Netherlands receive a 10-valent vaccine (Synflorix, GSK) instead of the previous 7-valent vaccine (Prevenar, Pfizer). At the end of 2013 the Dutch Health Council will issue new advice on the type of vaccine (PCV10 versus PCV13) to be administered and the vaccination schedule (2+1 versus 3+1).

5.11.3 Epidemiology

5.11.3.1 Disease

Data on the numbers of patients with IPD over time comes from the laboratory surveillance data of the Netherlands Reference laboratory for Bacterial Meningitis (NRBM). Nine sentinel laboratories covering approximately 25% of the Dutch population send in all pneumococcal isolates from cerebrospinal fluid and blood. The numbers reported below are extrapolated to the whole Dutch population.

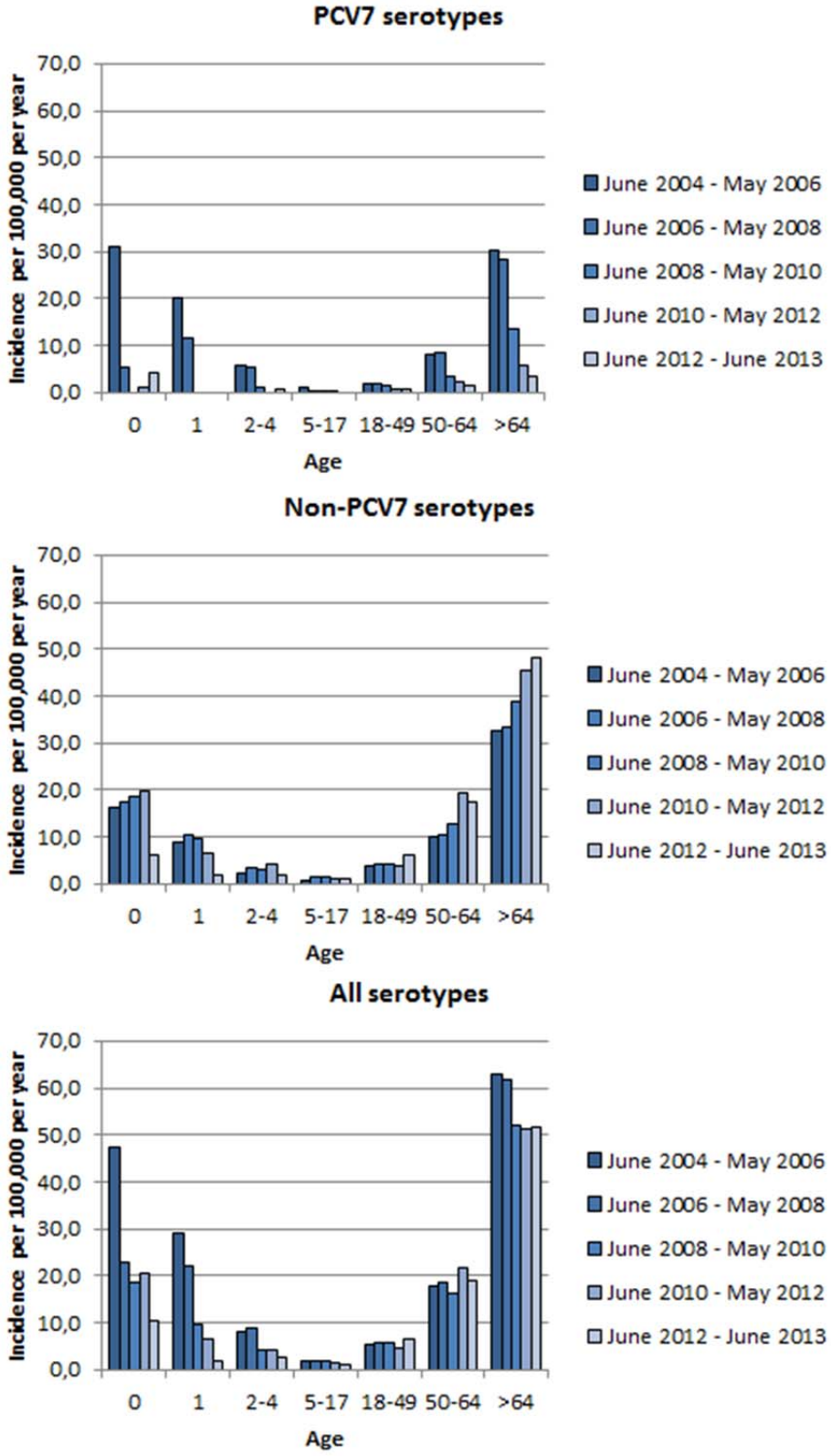


Figure 20 Incidence of IPD by age and time period (PCV7 was implemented in June 2006) for PCV7 serotypes (upper graph), non-PCV7 serotypes (middle graph) and all serotypes (lower graph). Note: numbers are extrapolated to the whole Dutch population.

The incidence of IPD caused by serotypes that were included in PCV7 decreased strongly in vaccinated as well as unvaccinated age groups after implementation of PCV7 in the NIP (Figure 20, upper graph; Figure 21, upper graphs). However, the incidence of IPD caused by non-PCV7 serotypes increased in the older age groups (Figure 20, middle graph; Figure 21, lower graphs). Overall, the incidence of IPD decreased in children below 5 years and in adults over 64 years of age (Figure 20, lower graph). In the other age groups, IPD incidence remained stable.

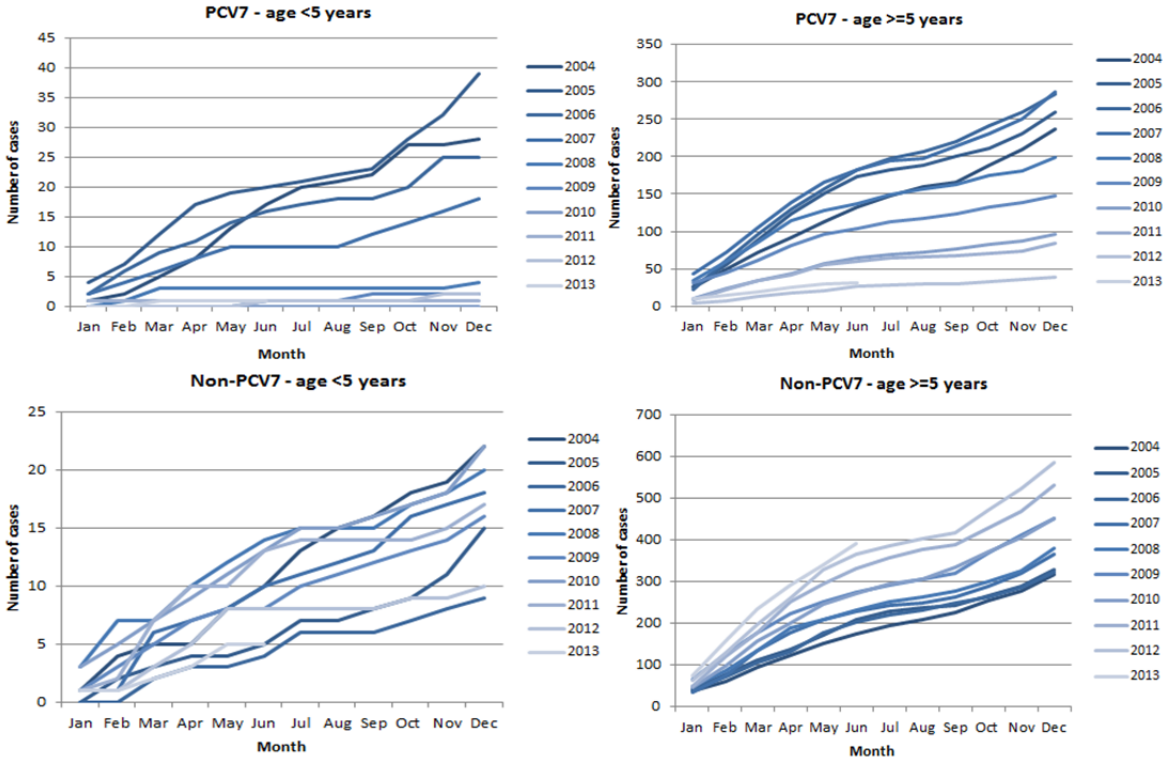


Figure 21 Cumulative number of IPD caused by PCV7 serotypes and non-PCV7 serotypes in the nine sentinel labs covering 25% of the Dutch population in children under five years of age and people of five years and older. Note that different scales are used in the graphs.

Since 2006, the NRBM has received isolates from all laboratories for children up to four years of age, therefore covering the whole Dutch population. The number of IPD cases caused by the additional serotypes included in PCV10 (serotype 1, 5 and 7F) decreased from 10–21 per year in 2007–2011 to 4 cases in 2012 and 2 cases in 2013 (until July) among children aged up to 1 year (Figure 22). This is probably due to the implementation of PCV10 in the NIP in May 2011. An analysis comparing vaccinated and unvaccinated birth cohorts showed a significant decrease in IPD caused by additional PCV10 serotypes (incidence rate ratio (95% CI) = 0.09 (0.01–0.69)). No effects on IPD caused by additional PCV10 serotypes have (yet) been seen in older age groups.

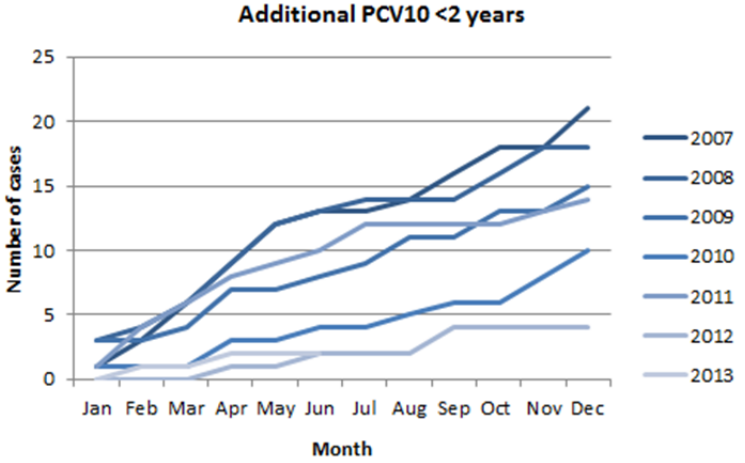


Figure 22 Cumulative number of IPD caused by additional PCV10 serotypes (1, 5 and 7F) in children under two years of age. Note: nation-wide data were used.

5.11.3.2 Vaccine effectiveness

From 2006 to July 2013, there were 12 children with vaccine type IPD who received at least two vaccinations (Table 9).

Table 9 Children with vaccine type IPD who received at least two vaccinations

Year of diagnosis	Age in months	Serotype	Number of vaccinations	Patient details if known
2008	3	9V	2	Diagnosis within 1 week following second dose
2008	3	6B	2	?
2008	7	6B	3	?
2009	29	19F	4	?
2009	6	19F	3	-
2010	12	6B	4	?
2011	59	19F	4	Nephrotic syndrome
2012	63	18C	4	-
2012	45	19F	4	Leukemia
2012	54	9V	4	?
2013	2	7F	2	Premature
2013	73	19F	4	?

5.11.4 Pathogen

No obvious changes in the characteristics of the pneumococcal strains isolated from patients with IPD were observed.

5.11.5 Adverse events

In the Netherlands in 2012, the number of AEFIs following pneumococcal vaccination reported to Lareb was 577, compared with 521 reports in 2011 (Lareb: http://www.lareb.nl/getmedia/9cc7480c-f4df-422a-a2fb-7841bc327290/Lareb-rapportage-rvp-2012-web.pdf). As pneumococcal vaccination was mostly administered simultaneously with DTaP-Hib-HepB vaccination, it is not known to which of the two vaccines the AEFI could be ascribed. It is noteworthy, however, that in the period 2005–2013 Lareb received ten reports of apnoea in preterm

infants with a gestational period of > 28 weeks, most latencies being reported within one day following immunisation. Even though it is not known whether all cases meet all the criteria for infant apnoea, it is remarkable that ten reports have been received, in view of the fact that the information leaflet for the pneumococcus vaccine, currently used in the Dutch childhood immunisation programme, refers only to apnoea following immunisation in very premature infants (≤28 weeks of gestation).

In an overview of international studies, Pomat et al. demonstrated that PCV7 is well-tolerated in neonates and young infants in Papua New Guinea [120]. The same applied when PCV7 was administrated simultaneously with *Haemophilus influenzae* type b conjugate vaccine [121].
Trials conducted to assess the safety and reactogenicity of PCV10 showed a good safety profile for this vaccine when co-administered with MenACWY-TT or DTaP-HBV-IPV/Hib [122, 123]. Furthermore, it was shown that this vaccine was well tolerated when given in different schedules and when administered as a booster dose in the second year of life [124, 125]. Studies conducted to compare the safety of PCV13 with PCV7 showed a similar or favourable safety profile of PCV13 [126-134], even when administered to children who had previously received PVC7 [135]. Tseng et al. identified potential signals for encephalopathy and Kawasaki disease following PCV13 vaccination. However, evaluation of these signals through medical record review failed to confirm PCV13-associated encephalopathy. The relative risk for Kawasaki disease in the 28 days following vaccination was 1.94 (95% CI 0.79–4.68), making PCV13 comparable to PCV7. Although it was not a significant finding, the authors concluded that the possible association of Kawasaki disease and PCV13 deserved further investigation [136].
In a trial conducted in HIV-infected, immunologically stable adults in South America, both PPV23 and PCV7 were found to be safe and well tolerated [137]. A phase I trial examined the safety of three doses of a pneumococcal single-antigen protein vaccine candidate (PlyD1). No vaccine-related SAEs or drop-outs due to an AE occurred [138]. In other phase I trials, promising safety profiles of monovalent and bivalent protein pneumococcal vaccine candidates were demonstrated in adult populations [139, 140].

5.11.6 Current/ongoing research

The PIM (Pneumokokken Iets Minder) study, a large randomised controlled trial, compared the immunogenicity of PCV13 between four internationally used vaccination schedules [141]. Infants (n=400) were randomly assigned to receive PCV13: at 2, 4 and 6 months of age (2-4-6); at 3 and 5 months (3-5); at 2, 3 and 4 months (2-3-4); or at 2 and 4 months (2-4), with a booster dose at 11.5 months of age. After the booster dose, there were no significant differences in antibody concentrations between the four schedules for almost all serotypes. After the primary series, the 2-4-6 schedule was superior to the 3-5, 2-3-4, and 2-4 schedules for 3, 9, and 11 serotypes, respectively. Of the reduced dose schedules, the 3-5 schedule performed better with regard to antibody response than the 2-4 schedule for 11 serotypes after the primary series.
The PIEN study compared humoral and cellular immunity between PCV10 and PCV13 before the booster dose (at 11 months) and after the booster dose (at 12 months). Before the booster vaccination PCV10 showed significantly higher antibody concentrations than PCV13 for serotypes 6B, 9V, 18C, 23F and 1, whereas PCV13 showed higher antibody concentrations for serotypes 19F, 3, 6A and 19A (the last three serotypes are not included in PCV10) (Figure 23 upper graph). In contrast, after the booster vaccination PCV13 showed significantly higher antibody concentrations for serotypes 6B, 9V, 14, 19F, 23F, 5, 3, 6A and

19A (Figure 23 lower graph). Children in the PCV10 group received their vaccinations at the Well Baby Clinics and therefore received the first three doses on average later than children in the PCV13 group, which could partly explain the higher antibody concentrations for PCV10 before the booster. However, the per protocol analysis, which included only children that were vaccinated in specific time windows, also showed higher antibody concentrations for PCV10 before the booster vaccination. For serotypes 6B, 19F, 1, 7F, 6A and 19A the numbers of plasma and memory cells were measured before and shortly after the booster vaccination. The number of plasma cells was not different between PCV10 and PCV13 after the booster dose. The number of memory B cells was higher for PCV13 than for PCV10 before and after the booster dose.

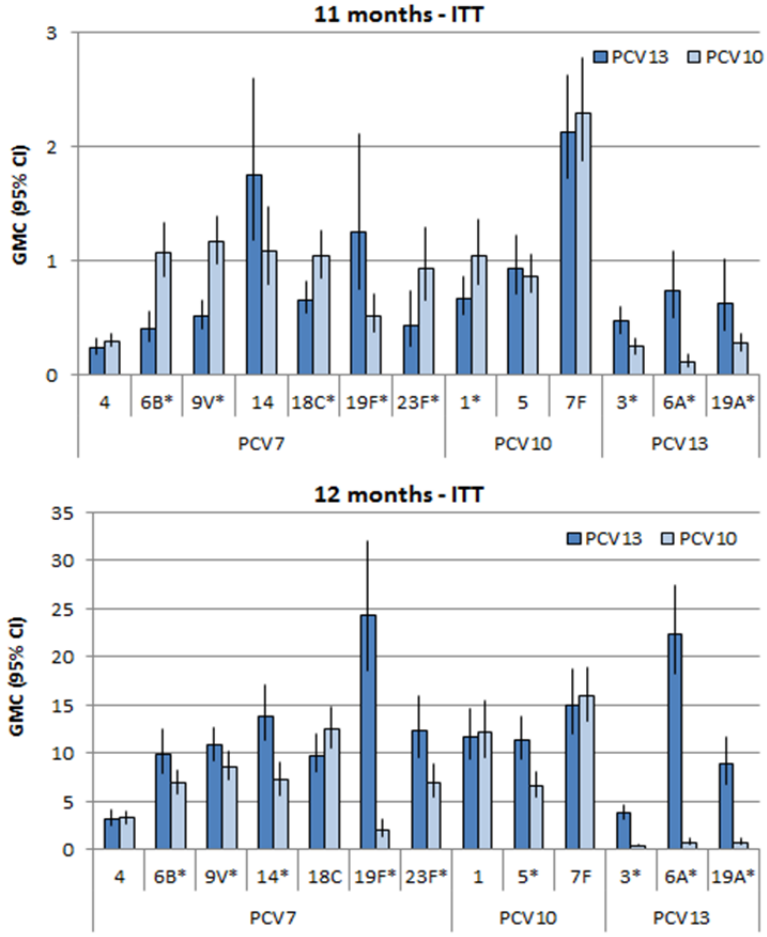


Figure 23 Geometric mean concentration (GMC) and 95% confidence intervals of serotype specific pneumococcal IgG levels for PCV13 and PCV10 before the booster vaccination at 11 months of age (upper graph) and after the booster vaccination at 12 months of age (lower graph)
*statistically significant difference between PCV13 and PCV10

The OKIDOKI-3 study assessed pneumococcal carriage in the nasopharynx 6.5 years after the introduction of PCV7 and 1.5 years after the introduction of PCV10. This study showed that 6.5 years after the implementation of PCV7 and 1.5 years after PCV7 had been replaced by PCV10, pneumococcal vaccination had resulted in a persistent reduction in and almost complete disappearance of carriage of vaccine-serotypes pneumococci in vaccinated children aged 11 months and 24 months. The impact of PCV10 on the carriage of the additional

serotypes 1, 5 and 7F in 11-month-old infants could not be demonstrated because the carriage prevalence of these invasive serotypes is usually low, unless there is an outbreak situation.
Currently, clinical data, including length of hospital stay and mortality, are collected from patients who were diagnosed with IPD between June 2010 and June 2012 at one of the nine sentinel laboratories which send isolates to the NRBM. Data from this study will be compared with similar data from patients with IPD before and after the introduction of PCV7 (June 2004 to June 2010). Also, the isolates collected by the nine sentinel laboratories between June 2010 and June 2012 are currently characterised by two molecular typing methods. Thereby, the composition of the pneumococcal population is assessed and will be compared with the composition of the pneumococcal population collected in 2004–2005 and 2008–2009. The results may indicate changes in the pneumococcal population due to selective pressure of the vaccine.

5.11.7 International developments

A cluster-randomised double-blind trial (FinIP) was performed in Finland evaluating the clinical efficacy of PCV10 in a 3+1 and a 2+1 vaccination schedule against invasive pneumococcal disease [125]. A total of 30,528 children aged under 19 months were included and received either PCV10 or hepatitis vaccine. Furthermore, infants aged under 7 months received either a 3+1 or a 2+1 schedule. Vaccine type IPD was diagnosed in 13 participants: none in the PCV10 3+1 group, one in the PCV10 2+1 group and 12 in the control groups. Vaccine effectiveness was 100% (95% CI 83–100) for PCV10 3+1 and 92% (58–100) for PCV10 2+1. This is the only study that has assessed the clinical efficacy of PCV10 in a reduced dose schedule.

The widespread use of polysaccharide conjugate vaccines has led to a significant decrease in invasive pneumococcal disease caused by vaccine serotypes, but an increase in disease caused by non-vaccine serotypes, which has resulted in a diminished overall efficacy of these vaccines. A solution to this problem would be the development of a serotype-independent pneumococcal vaccine. This can be accomplished by the development of a vaccine based on protein antigens, whole pneumococci or recombinant bacteria containing pneumococcal antigens. Several proteins have been proposed for use in pneumococcal vaccine development, such as pneumolysin, pneumococcal surface protein A, pneumococcal surface protein C and pneumococcal surface antigen A. Recently, new antigens have been described through high-throughput screenings, including virulence factors and adhesins [142]. An efficient protein vaccine will probably have to be composed of a mixture of various proteins to overcome problems such as antigen variability, differences in expression levels and the possibility of immune escape. Human trials with these serotype-independent pneumococcal vaccines have already been performed or are ongoing. The pneumococcal surface protein A (PspA) was the first protein tested in humans and showed induction of anti-PspA IgG antibodies in serum after i.m. vaccination with alum as adjuvant. However, after the initial success with PCV7 in clinical trials and subsequent licensing of this vaccine, interest in other vaccines declined and clinical trials of serotype-independent pneumococcal vaccines faded. Recently, because of the replacement of non-vaccine serotypes, interest in these vaccines has risen again and new clinical trials have been initiated. Most of the results of these trials are not yet available in literature; only results from a few phase I/II studies have been published. These studies were performed with protein-based vaccines or whole-cell pneumococcal vaccines [142]. It would be interesting to follow which of these non-serotype pneumococcal vaccines are promising enough to enter phase III trials.

5.11.7.1 Cost-effectiveness

Several European countries have included PCV13 in their national immunisation programmes using a paediatric 2+1 or 3+1 dosing schedule [143]. The RIVM performed an economic evaluation comparing PCV13 with the current PCV10 vaccination. Based on a previously developed model and using the most recent epidemiological data available, including indirect effects, the expected health outcomes, costs and ICER were estimated. The results in the base case analysis showed that with the present four-dose vaccination schedule, PCV10 is the preferred option in terms of reduced costs and better health outcomes. Including PCV13 in the NIP would prevent additional cases of meningitis and bacteremia among children, since it prevents disease against three extra serotypes. However, the model predicted that the impact of PCV10 on acute otitis media (AOM) would far outweigh that of PCV13 given the large volume of AOM cases prevented by PCV10. Using a three dose schedule in the base case situation, the ICER of implementing PCV13 compared with PCV10 was € 30,000 per QALY gained; applying the same vaccine price, PCV13 proved to be the cost-saving option. This is in line with the recent findings of Stoecker et al. who evaluated the cost-effectiveness of using 2 versus 3 primary doses of PCV13 [144]. Removing a dose from the primary PCV13 series would lead to a modest increase in pneumococcal diseases and substantial societal cost savings.
In the past years, several economic evaluations have been published comparing the cost-effectiveness of infant vaccination of PCV10 with PCV13 [145-151]. The studies show opposite results either in favour of PCV10 or in favour of PCV13, even when the cost-effectiveness in one country was assessed [145, 148]. Farkouh et al. stated in a review article that differences in outcomes were mainly due to differences in input parameters such as assumptions regarding effects on AOM, indirect effects and the use of epidemiology data [152]. The lack of scientific evidence on the efficacy of PCV13 and the unknown long-term direct and indirect effects of vaccination make it difficult for policy-makers in many countries to decide whether to select PCV10 or PCV13 as part of their national immunisation programmes.

5.12 Human papillomavirus (HPV) infection

T.M. Schurink-van 't Klooster, M. Mollers, A.J. King, M.A. Vink, W. Luytjes, J.M. Kemmeren, F.R.M. van der Klis, H.J. Vriend, A.W.M. Suijkerbuijk, J.A. Bogaards, H.E. de Melker

5.12.1 Key points

- Slightly increasing incidences of HPV-associated cancers have been found in the Netherlands in the last decade.
- Mathematical modelling estimates that the HPV-related cancer burden among males is reduced by approximately one-third at the current vaccine uptake of 60%, and by two-thirds at a sustainable 90% uptake among pre-adolescent girls.
- The cumulative incidence of HPV for vaccinated and unvaccinated girls in a cohort study among girls eligible for HPV vaccination at 36 months was 23.1% for any HPV type and 14.2% for high risk HPV types. The cumulative persistence at 36 months was 5.8% for any HPV and 2.8% for high risk HPV.
- A study among visitors to STI clinics showed that HPV DNA positivity and HPV antibody seropositivity were higher in women than in men. The

association between type-specific DNA and serum antibodies was similar across gender.
- The reporting rate of adverse events for 2012 is clearly higher compared to the reporting rate of 2011, but comparable with the reporting rate of 2010.
- No statistically significant association between HPV vaccination and migraine was found using different kinds of analysis, although numbers were low.

5.12.2 Changes to the vaccine 2012–2013

No changes were made to the HPV vaccine used in the NIP. Cervarix® was offered within the NIP to all girls at 12 years of age in a three dose schedule: at 0, 1 and 6 months.

5.12.3 Epidemiology

5.12.3.1 HPV associated cancers

Besides cervical cancer, HPV infection can also be related to vaginal, vulvar, penile, anal, mouth/oral and oropharyngeal cancer. In Europe, non-cervical cancers contribute substantially to the economic burden of HPV-related cancers [153]. The incidence of cases and deaths due to these cancers in the Netherlands is presented in Table 10 and Table 11. HPVs are estimated to cause 90–93% of anal cancers, 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 [154]. Incidences of HPV-associated cancers have slightly increased in the last decade in the Netherlands.

Table 10 Incidence / 100,000 (standardised by the European standardised rate) of new cervical, anogenital, mouth/oral and pharynx/pharyngeal cancer cases in the Netherlands 2000–2011, by cancer type (The Netherlands Cancer Registry (NKR))

Cancer type		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Cervix		7.48	6.55	7.06	6.48	7.51	7.29	7.35	7.98	7.62	7.63	7.84	7.93
Ano-genital	-Vulva/vagina	2.52	2.60	2.57	2.82	2.74	2.74	2.90	3.31	3.04	3.52	3.47	3.83
	- Penis	0.97	1.18	1.27	1.23	1.39	1.25	1.31	1.23	1.39	1.46	1.44	1.41
	- Anus	0.64	0.69	0.61	0.73	0.57	0.70	0.80	0.72	0.81	0.81	0.84	0.87
Mouth		4.47	4.50	4.43	4.84	4.78	4.95	4.64	4.60	4.72	4.88	5.08	4.82
Pharynx		3.13	3.12	3.09	3.09	3.20	3.01	3.09	2.99	3.40	3.38	3.15	3.35

Table 11 Incidence / 100,000 of deaths related to cervical, anogenital, mouth, oropharynx and pharynx cancer cases in the Netherlands 2000–2012, by cancer type (Statistics Netherlands (CBS))

Cancer type		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
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	2.55
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	1.46
	- 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	0.46
	- 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	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	1.55
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	0.75
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	1.82	1.85

* Number of deaths due to pharynx cancer includes number of oropharynx cancer deaths.

5.12.3.2 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) centres was 2308 in 2012, corresponding to an estimated positivity rate of 1.9% (numerator is total number of STI visits). The highest positivity rate was found among heterosexual men (2.5%) and the lowest among women (1.4%). The number of diagnoses of genital warts reported to GPs was estimated at 24,007 in 2011 (50% men and 50% women), an increase of 13% over 2010. The number of diagnoses of genital warts among women increased more sharly: by 21% compared with 2010 [155].

5.12.4 Adverse events

During 2012, Lareb received 104 spontaneous reports of AEs following vaccination against HPV. Eleven of them were SAEs [68]. The reporting rate for 2012 was higher than the reporting rate for 2011 (n=51) but comparable with the reporting rate for 2010 (n=129) [156]. The decline in 2011 may have been caused by the transition of the surveillance system from the RIVM to Lareb on 1/1/2011. More remarkable was the increase in reports in 2012 of (chronic) fatigue after vaccination with HPV. Most reports were concentrated in the period following an article in a national newspaper: 46 messages within 6 weeks. Thirty of the reports concerned vaccinations in previous years. Based on additional analyses, it cannot be concluded whether there is a possible association between HPV vaccine and fatigue. In a study in the UK, no association was found between vaccination with bivalent HPV vaccine and an increased risk of chronic fatigue syndrome [157]. Despite this finding, the occurrence of long-lasting fatigue will be further monitored in the Netherlands.

In the literature, the safety and tolerability of the bivalent HPV (HPV2) vaccine was demonstrated in women aged 25, although fever and local pain were more frequently registered in these women than in adolescent girls [158]. HPV2 was also well tolerated in patients with juvenile idiopathic arthritis and in healthy female adolescents [159]. Moscicki et al. assessed the reactogenicity of a booster dose of HPV2 in women who had received three doses of HPV2 seven years earlier. The reactogenicity of this fourth dose was comparable with that of the first dose [160].
Several studies assessed the safety of the quadrivalent HPV (HPV4) vaccine. Previously, a post-marketing surveillance study using data on spontaneous reports of AEs data in the US suggested that Guillain-Barre syndrome is reported more frequently following HPV4 vaccination [161] which contradicted other studies on the topic [162, 163]. Recently, however, Ojha et al. did not find an association between HPV4 vaccination and the occurrence of Guillain-Barre syndrome among vaccine-eligible females or males in the US [164]. Furthermore, HPV4 seems generally safe and well tolerated in young black women [165], in adolescents and young women with Systemic lupus erythematodes (SLE) [166] and in HIV-infected women [167]. Furthermore, the CDC indicated from safety monitoring data that HPV4 is safe [168].
Intradermal administration of HPV vaccines could be dose-sparing and cost-saving. A pilot randomised study showed that intradermal administration of either HPV2 or HPV4 raised no safety concerns but was more reactogenic than intramuscular administration, although still tolerable [169].

5.12.5 Current/ongoing research

5.12.5.1 HPV DNA

HPV prevalence among young girls (HAVANA study)
A prospective cohort study which was initiated in 2009 among vaccinated and unvaccinated 14- to 16–year-old girls is still ongoing. The primary aim is to monitor the effect of vaccination on HPV-type distribution amongst these two groups. Therefore, vaginal self-swabs collected in this cohort were tested for the presence of HPV DNA. Until now, four rounds have been completed. The cumulative incidence at 36 months (n=1,077) was 23.1% (95% CI 20.6%–25.6%) for anyHPV and 14.2% (95% CI 12.1%–16.3%) for high-risk HPV (hrHPV). The cumulative persistence at 36 months among 1097 girls was 5.8% (95% CI 4.4%–7.2%) for anyHPV and 2.8% (95% CI 1.8%–3.8%) for hrHPV. Type-specific incidence rates ranged from 0.1/100 person-years (95% CI 0.0–0.2) for HPV34, -35, -44 and -70 to 2.0/100 person-years (95% CI 1.7–2.5) for HPV51. Type-specific persistence rates ranged from 0/100 person-years for HPV45, -34, -40, -44, -70 and -74 to 0.3/100 person-years (95% CI 0.2–0.6) for HPV51, -52 and -66.

HPV prevalence among young STI clinic attendees (PASSYON study)
To monitor possible changes in HPV dynamics over time in the post-vaccination era compared with pre-vaccination era, a biennial cross-sectional study of 16- to 24-year-old male and female STI clinic attendees was set up [170]. In 2009, 2011 and 2013, the first three rounds of this study took place in a selection of STI clinics throughout the Netherlands. The anogenital samples collected were analysed for the presence of HPV DNA and the specific HPV type was determined. Results from the first round showed high prevalence rates (any HPV 67%) [170]. Females had higher HPV prevalence rates than males (72% versus 54%) and were more often infected with an hrHPV type. In addition, HPV16/18 was more commonly detected in females than in males (23% versus 16%). HrHPV infection was especially related with high-risk sexual behaviour in contrast to low-risk HPV (lrHPV) types. The results of the second round (2011) showed similar prevalence rates and related behavioural factors. Results from the third round are not yet available. This study is ongoing.

HPV and genetic variability in HPV16 L1 sequence
Intratypic molecular variants of HPV types 16 and -18 are known to occur and are distributed differently within the five continents. In the Netherlands, a bivalent vaccine composed of recombinant L1 proteins from HPV16 and -18, has been used to prevent cervical cancer since 2009. Long-term vaccination with L1 proteins may lead to selection for viruses with genetic variants of the L1 protein and thus to changes in the HPV16 and -18 virus population. In order to be able to detect possible changes, knowledge of the genetic variability of the L1 gene in HPV16 and -18 viruses circulating in the Netherlands at the start of vaccination is required. In this study we aim to investigate the genetic variability in the major capsid L1 gene in HPV16 and -18 viruses currently circulating in the Netherlands. Therefore, DNA samples obtained from swabs collected in 2009 and 2011 within the PASSYON (PApillomavirus Surveillance among STI clinic Youngsters) study among Dutch 16- to 24-year old male and female attendees of the STI clinics were used for additional DNA sequencing. Recently the RIVM has set up an assay for amplification of the entire L1 gene on clinical anogenital swabs followed by DNA sequencing. Results of HPV16 L1-gene-sequencing revealed 95 single nucleotide polymorphisms (SNPs; 68 silent and 27 non-silent mutations) in all samples. The majority of the HPV16 isolates (198/213, 93%) were closely related to the European/Asian types and 16/213 (7%) to the

African variants. The most common L1 sequence found was detected in 31% of the samples and was very similar to the reference strain differing in only two positions with silent mutations. The majority of the non-silent mutations (17/27, 63%) were located in sequences encoding alpha helix, beta sheet or surface loops, in particular in the immunodominant FG loop, and may influence the secondary protein structure. Overall, this study provides unique pre-vaccination data on the genetic variation of the L1 gene of HPV16 viruses circulating in the Netherlands among adolescents and young adults. Analysis of the genetic variability of HPV18 is still ongoing.

5.12.5.2 Serology

HPV DNA and antibody positivity

To assess the impact of HPV vaccination on HPV infection dynamics in the Netherlands data from the first two rounds of the previously described PASSYON study (see section 5.12.5.1) were analysed for type-specific HPV DNA and HPV-specific antibody (Ab) positivity rates of seven main carcinogenic HPV types. In addition, associations between (type-specific) DNA and antibody positivity were studied [171].

Positivity rates were high in this young and sexually active population without the benefit of HPV vaccination. HPV DNA positivity and HPV antibody seropositivity were higher in women than in heterosexual men, with men who have sex with men (MSM) in between, but the association between the detection of type-specific DNA and serum antibodies was similar across gender.

It was hypothesised that the dry, keratinized tissue of the penis is much harder for the virus to infect than the soft, mucosal tissue of the vagina or the anus. Therefore, gender differences observed in HPV DNA positivity and HPV Ab seropositivity may be related to the type of tissue being infected, penile infections resulting less often in a humoral response than vaginal and anal infections.

Characteristics of HPV-specific antibody responses induced by infection and vaccination

Immunological studies have shown that naturally derived antibodies differ from vaccine derived antibodies in avidity capacity. Antibodies derived from vaccination have a higher avidity capacity than naturally derived antibodies. In addition, antibodies are mainly from the IgG1 and -3 subclasses no matter how the antibodies are derived [172].

Immunogenicity of the bivalent HPV vaccine in adolescents with immunological disorders

Studies among young women with immunological disorders, e.g. juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus (SLE), have shown that HPV vaccination is safe with high seropositivity rates and strong HPV16/18-specific antibody responses in female adolescents with JIA – results being comparable to those in healthy female adolescents. The quality of the HPV-specific antibodies measured by their avidity and the kinetics of the HPV16/18-specific memory B-cell responses were similar in patients and healthy controls, although the magnitude of B-cell responses up to one year after vaccination tended to be lower in patients [159].

The bivalent vaccine seems to induce markedly lower HPV16/18-specific antibody concentrations in female adolescents with SLE than in healthy controls [173].

5.12.5.3 Vaccine uptake

Incomplete participation for HPV vaccination
According to the vaccination registry (Præventis, RIVM), 3,277 girls from cohort 1997 started HPV vaccination but did not complete the whole series. Of them, 643 (20%) filled in a questionnaire on factors which had affected the participation of the girls.
Thirteen percent of the participants indicated that they were fully vaccinated; to verify this we asked them to send us a copy of their vaccination certificate. For participants who had received only one or two doses, the main reason for incomplete vaccination that they had not received an invitation (29%). The next most indicated reasons were 'forgot' (20%), 'no time' (8%) and 'sickness' (7%). In addition, 17% of the girls reported that bad experiences and/or AEs by earlier vaccinations had influenced (a little to very much) their incomplete vaccination. Moreover, in response to the invitation to participate in this study, 28 girls (or a parent) contacted us because they wanted to complete the series.

5.12.5.4 Safety

Association between HPV vaccination and migraine
Following earlier research where incidences of migraine in pre- and post-vaccination years were compared, we conducted an analysis of the association between HPV vaccination and migraine (Schurink-van 't Klooster, manuscript in preparation). Potential incident migraine cases were selected from a longitudinal observational electronic database of medical records from Dutch GPs (Integrated Primary Care Information (IPCI), Erasmus MC Rotterdam). Potential cases were selected if the record contained the International Classification of Primary Care (ICPC) code N89 or 'migrai*' in the free text within the period 2009–2010. Selected cases were manually validated and coded. Girls born in 1993–1997 (i.e. who were eligible for HPV vaccination in 2009–2010) from the IPCI database were linked to the vaccination registry (Præventis, RIVM) to determine their HPV vaccination status.
No statistically significant higher risk of migraine was found in high-risk periods (six weeks after each dose) versus non-high-risk periods, with a relative risk (RR) of certain migraine of 4.3 (95% CI 0.69–26.6) and for certain + probable migraine of 2.9 (95% CI 0.71–11.7). Furthermore, mortality rate ratios (MRRs) for migraine in monthly periods following vaccination compared with migraine in unvaccinated girls ranged from 0.0 to 3.0; none was statistically significant. Thus, no statistically significant association between HPV vaccination and migraine was found using different kinds of analysis. However, numbers of cases were rather low.

5.12.5.5 Modelling

Impact of the current vaccination programme on the burden of HPV-related disease among men
The impact of the current female-only vaccination programme on the burden of HPV-related disease among men has been further explored by mathematical modelling. Reductions in HPV prevalence among male heterosexuals were calculated on the basis of a type-specific transmission model, which had already been used to assess the long-term impact of vaccination on HPV-related disease among women. HPV16 and HPV18 infection risk reductions were subsequently projected onto those HPV-related cancers that are not attributable to MSM. The latter quantity was estimated from the prevalence of MSM in the Dutch population and from the relative risk of anogenital and oropharyngeal cancers in MSM relative to heterosexual males, as reported for the Danish population

[174]. In terms of QALYs lost, we estimate that the HPV-related cancer burden among males will be reduced by approximately one-third at the current vaccine uptake of 60%, and by two-thirds at a sustainable 90% uptake among pre-adolescent girls. Furthermore, at increased female vaccine uptake, the male disease burden will become dominated by anal cancer, underscoring the relevance of HPV prevention efforts for MSM.

Serological data to monitor HPV vaccination
As the duration from HPV infection to cervical cancer development is on average almost 27 years [175], it may take a couple of decades before the first effects of vaccination on numbers of cervical cancer cases become apparent. Monitoring of surrogate endpoints of HPV disease is required and data from serological surveys (e.g. the PIENTER studies [11, 12]) might be a useful tool for observing changes in the infection dynamics of HPV. Serological data from the PIENTER studies have been analysed before, using a cut-off value to denote whether a person was seropositive [176]. However, the serological reaction to an HPV infection is weak and does not lead to a clear threshold between seropositives and seronegatives. As a result, using a threshold might lead to misclassification bias. We developed a statistical model to re-analyse HPV16 serology using antibody concentrations from the PIENTER-2 study. We estimated that seroprevalence for men and women would increase with age, with a steep increase around adolescence which corresponds with a similar increase in sexual activity. Besides, seroprevalence among men would keep increasing, whereas seroprevalence in women would decrease from the age of 40 years onwards. We found a gender-specific serological response with women having higher HPV16 antibody concentrations than men. We can use these new seroprevalence figures as a benchmark for future serological surveys to monitor changes in infection dynamics due to the introduction of HPV vaccination.

5.12.5.6 Cost-effectiveness

In the past year, two economic evaluations of HPV vaccination in the Netherlands have been published. Luttjeboer estimated the maximum health and economic benefits of vaccinating 12-year old girls against infection with HPV, taking cross-protection and non-cervical cancers into account. For this purpose, a static model was built to estimate the cost per QALY. Besides cervical cancer, HPV can cause cancers in the oropharynx, vulva, vagina and the anus/anal area [177]. In the base-case, she found ICER of €5815 per QALY. The robustness of this result was examined in a sensitivity analysis. The ICER proved to be most sensitive to vaccine price, discounting rates, the costs of cervical cancer and variation in the disutility of cervical cancer. In conclusion, evidence on cross-protection and protection against precancerous lesions of the vulva and the vagina supports the idea that the health and economic benefits of vaccinating against HPV go beyond cervical (pre-) cancer states (for types 16 and 18 only).
Westra assessed the cost-effectiveness of the bivalent and quadrivalent vaccine, including the additional benefits of cross-protection and protection against genital warts, in comparison with a screening-only strategy [178]. Both vaccines provide cross-protection against HPV types not included in the vaccines. In a cohort of 100,000 women, using a Markov model, implementation of the bivalent or quadrivalent vaccine reduces the cervical cancer incidence by 221 and 207 cases annually, corresponding to ICERs of € 17,600/QALY and € 18,900/QALY, respectively. It was estimated that the quadrivalent vaccine additionally prevents 4,390 cases of genital warts annually, reducing the ICER to € 16,300/QALY. HPV vaccination has been implemented for the prevention of

cervical cancer. From this perspective, use of the bivalent HPV vaccine appears to be more effective and cost-effective. Including the benefits of prevention against genital warts, the ICER of the quadrivalent HPV vaccine was found to be slightly more favourable.
Brisson also compared the cost-effectiveness of the quadrivalent and bivalent HPV vaccines, based on a dynamic transmission model of HPV infection and disease (anogenital warts, and cervical, anogenital and oropharyngeal cancers) [179]. Under base-case assumptions (vaccinating ten-year-old girls, 80% coverage, $ 95/dose), using the quadrivalent and bivalent vaccines is estimated to cost $ 15,528 and $ 20,182 per QALY gained, respectively. In this study, at equal price, the quadrivalent vaccine is more cost-effective than the bivalent under all the scenarios investigated, except when assuming a longer duration of protection for the bivalent and minimal anogenital warts burden. Vaccinating pre-adolescent girls against HPV is predicted to be highly cost-effective.
Schobert adapted an HPV dynamic transmission model which had been used in other countries, to the German context [180]. The model was used to compare a strategy of combining the vaccination of females aged 12–17 years old and cervical cancer screening with a cervical cancer screening only strategy, based on the current recommendations in Germany. In addition, the impact of increasing vaccination coverage in this cohort of females aged 12–17 years was evaluated in a sensitivity analysis. He found that the current quadrivalent HPV vaccination programme for females aged 12 to 17 in Germany is cost-effective with an ICER of € 5,525/QALY. The ICER increased to € 10,293/QALY when the vaccine effects on HPV6/11 diseases were excluded. At steady state, the model predicted that vaccinating girls aged 12-17 could reduce the number of HPV6/11/16/18-related cervical cancers by 65% and genital warts among women and men by 70% and 48%, respectively. These results show that the current quadrivalent HPV vaccination and cervical cancer screening programmes in Germany will substantially reduce the incidence of cervical cancer, cervical intraepithelial neoplasia and genital warts. The evaluated vaccination strategies were all found to be cost-effective.
HPV vaccination programmes primarily targets young girls before sexual debut. Demarteau assessed whether vaccination with the HPV16/18 AS04-adjuvanted vaccine in addition to screening remains cost-effective in females after sexual debut compared with screening alone in Belgium [181]. The role of protection against non-HPV16/18 was also investigated. The model estimated that vaccinating a cohort of 100,000 girls at age 12 would prevent 646 cervical cancer cases over a lifetime (102 non-HPV16/18) with an ICER of € 9171/QALY. Vaccinating at age 26 would prevent 340 cases (40 non-HPV16/18) with an ICER of € 17,348/QALY and vaccinating at age 40 would prevent 146 cases (17 non-HPV16/18) with an ICER of € 42,847/QALY. She concluded that extending HPV vaccination to females' post-sexual debut could lead to a substantial reduction in cervical cancer-related burden and would be cost-effective in Belgium.
Jiang conducted a critical review of cost-effectiveness analyses of HPV vaccination in males; nine studies were identified [182]. Due to the heterogeneity of these studies, limited conclusions can be drawn with regard to general cost-effectiveness. Nevertheless, key drivers were identified. More favourable cost-effectiveness appeared when all HPV-related diseases outcomes were considered and a suboptimal vaccine coverage among girls and/or lower vaccine prices were assumed.
In contrast to the above-mentioned studies above, Wilyman argued in a review that HPV vaccination programmes are not cost-effective since Pap screening will still be required in vaccinated women, especially in countries where regular Pap screening and surgery has already reduced the burden of this disease [183]. The author mentioned that vaccine costs are high and vaccination does not protect

against ~30% of cervical cancer. Wilyman concluded that it is necessary to examine the assumptions used in economic evaluations to be certain of the health benefits that are predicted.

5.12.6 Other relevant (international) developments

5.12.6.1 Current status of male HPV vaccination

Insights into the burden of HPV-related disease among men prompted Australia – the first country to introduce a government-funded HPV immunisation campaign – to vaccinate boys as well as girls in school-based cohorts from 2013 onwards [184]. This decision was taken once the efficacy of the quadrivalent HPV vaccine in preventing external genital lesions and anal intraepithelial neoplasia in males as well as females had been verified [185, 186]. Formal cost-effectiveness analyses to support this decision have not been made publicly available [187].
In the US, the routine use of quadrivalent HPV vaccine in boys aged 11–12 years has been recommended. In addition, catch-up vaccination of males aged 13–21 years has been recommended. In their recommendations, the Advisory Committee on Immunization Practices considered information on vaccine efficacy, safety, HPV-related disease incidence and mortality, cost-effectiveness and programmatic considerations [188]. While it was acknowledged that male vaccination is less cost-effective than a strategy of increased vaccine coverage of females, the inclusion of 12-year-old boys was deemed cost-effective at the current vaccine price and coverage in female-only vaccination programmes in the US.
In Europe, government-funded HPV immunisation programmes are still solely directed at females. The quadrivalent HPV vaccine has nonetheless been licensed for use in males up to 26 years of age by the European Medicines Agency. Interestingly, GlaxoSmithKline (GSK) is currently sponsoring a community-randomised phase IV vaccine trial in Finland (HPV040), comparing the population-level effectiveness of gender-neutral versus female-only vaccination. In this trial, 33 communities (comprising 80,000 eligible adolescents) were randomised into three groups: (i) bivalent HPV vaccine for girls only and hepatitis B vaccine for boys; (ii) bivalent HPV vaccine for girls and boys; (iii) hepatitis B vaccine for girls and boys. As of 2010, about 35,000 early adolescents were enrolled. The primary endpoint of the trial is high-risk HPV prevalence by birth cohort in 18-year-olds. Results are scheduled to appear in 2014.

5.12.6.2 Early effects of HPV vaccination

Since the introduction of the bivalent HPV vaccine in 2008 in England a reduction in genital warts diagnoses at genitourinary medicine clinics has been observed [189]. The overall reduction was 13.3% among 16–19-year-old females. The decline in genital warts diagnoses was positively associated with the estimated HPV immunisation coverage. Among GP diagnoses of genital warts, a similar pattern was seen. In addition, the efficacy of bivalent HPV vaccine against six months persistent infection with low-risk HPV types was estimated [190]. This trial showed an efficacy for HPV6/11 of 34.5% (95% CI 11.3–51.8) in HPV-naïve vaccinated (at least one dose) girls.
In Australia, the first population impact on cervical abnormalities was seen five years after the introduction of a vaccination programme using quadrivalent HPV vaccine [191]. In a population who attended screening and were eligible for school-based vaccination, histologically confirmed high-grade cervical abnormalities and high-grade cytology were less detected in vaccinated (any

dose) women than in unvaccinated women, i.e. HR 0.72 (85% CI 0.58–0.91) and HR 0.75 (95% CI 0.65–0.87), respectively.

5.12.6.3 Two-dose vaccination schedule versus three-dose schedule

Dobson et al. reported the results of a clinical trial in which the immunogenicity of two doses of quadrivalent HPV vaccine versus three doses was studied [192]. They found non-inferiority of GMT ratios for HPV types 6, 11, 16 and 18 one month after the last dose in 9-13-year-old girls who had received two doses compared with 9–13-year old girls who had received three doses. However, GMTs were significantly lower for HPV18 at month 24 and for HPV6 at month 36 in girls who had received two doses than in girls who had received three doses. Comparable results were found earlier for the bivalent vaccine. Romanowski et al. found that the licensed two-dose schedule was non-inferior for HPV types 16 and 18 in girls aged 9–14 years and 15–19 years compared with the three-dose schedule in 15–25-year-old girls [193]. Nevertheless, 9–14-year-old girls following the two-dose schedule had significant lower GMTs for HPV16 than those on the three-dose schedule. Kreimer et al. showed a similar vaccine efficacy against incident 12-month persistent HPV16 or -18 infections among 18–25-year-old women who had received two doses than among women who had received three doses [194].
It is unknown what the lower antibody responses mean in terms of duration of protection. A two-dose schedule (at 0 and 6 months) is approved for the bivalent vaccine in girls 9–14 years of age in nine low-income countries [195].

5.12.6.4 9-valent HPV vaccine

A new vaccine has been developed which protects against five more HPV types (31, 33, 45, 52, 58) – in addition to the four types included in quadrivalent vaccine (6, 11, 16, 18). The vaccine may prevent almost 90% of cervical cancer cases. In a phase IIb/III trial, 9-valent vaccine showed non-inferior GMT responses compared with quadrivalent vaccine in women aged 16–26 years and girls and boys aged 9–15 years [196]. Furthermore, the vaccine was found to be highly immunogenic to the five additional HPV types. In 16–26-year-old women, efficacy against HPV31/33/45/52/58-related high-grade cervical/vulvar/ vaginal disease was 96.7% (95%CI 80.9–99.8; per protocol analysis), and 96.0% (95%CI 94.4–97.2; per protocol analysis) against HPV31/33/45/52/58-related six-month persistent infection [197]. In addition, a non-inferior efficacy of 9-valent vaccine was shown for HPV16/18-related persistent infection compared to quadrivalent vaccine. The safety profile of the 9-valent HPV vaccine was generally comparable to that of the quadrivalent vaccine, except for the incidence of injection site reactions up to 15 days following vaccination in women aged 16-26 years (90.8% for 9-valent vaccine versus 85.1% for quadrivalent vaccine [198, 199].

6 Future NIP candidates

6.1 Rotavirus infection

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

6.1.1 Key points

- After a rise in the incidence of rotavirus associated gastroenteritis seen in the Netherlands in the previous few years, the decrease in 2011 continued in 2012.
- In 2012, G1P[8], G9P[8], G3P[8] and G4P[8] were most commonly found in the Netherlands.

6.1.2 Epidemiology

The Working Group Clinical Virology reports the number of rotavirus positive results weekly (see Appendix 1). After an increase in the number of rotavirus positive samples between 2007 and 2010 (2010: 2180 isolates), the decrease of last year (2011: 1504 isolates) was continued in 2012 (1287 isolates). The number of estimated hospitalisations due to rotavirus among children aged four years or younger has also decreased over the last two years, with the number of hospitalisations in 2012 (n=3,112) less than half of that of 2010 (n=6,442; 2011: n=4,487).

6.1.3 Pathogen

The Centre for Infectious Disease Research, Diagnostics and Screening (IDS) of the RIVM received 263 faeces samples that tested positive for rotavirus in peripheral laboratories; 256 samples also tested positive in the PCR performed at the IDS and 253 could be typed. G1P[8] is most commonly found, although it seems to follow a two-year cycle: in 2009 and 2011, G1P[8] was detected in 66% and 67%, respectively, of the isolates, compared with 48% in 2010 and 21% in 2012. In 2013, another peak in G1P[8] is expected, as an increase was already seen in December 2012. Other important types were G9P[8], G3P[8] and G4P[8]. G12P[8] was as common in 2011 as G9P[8] but was hardly seen in 2012, whereas G9P[8] remained. Co-infections with two types of rotavirus were detected in 20 samples (8%). Faeces samples came in throughout the year, but with a clear peak at the beginning of the year in accordance with observations in the previous years.

6.1.4 Adverse events

Oral rhesus/rhesus-human reassortant rotavirus tetravalent vaccine (RRV-TV) was licensed in 1998 but withdrawn in 1999 due to a rare association with intussusception, which occurred disproportionately in infants receiving their first dose at ≥90 days of age. Armah et al. examined RRV-TV for the prevention of rotavirus gastroenteritis, infants receiving the first dose during the neonatal period and the second before 60 days of age [200]. Rates of frequent AEs recorded after administration of RRV-TV or placebo were similar between treatment groups and all SAEs were judged to be unrelated to study intervention. No cases with intussusception were found.
Publications in recent years have demonstrated a low-level increased risk of intussusception after rotavirus vaccination [201, 202]. However, several studies published this year, including phase I, II and III trials, did not find increased risk

for SAEs including intussusception following Rotarix [203-207]. For Rotateq a persistent clustering of reported intussusception events between three and six days after the first dose of this vaccine was observed. This clustering could translate into a small increased risk of intussusception with a reporting rate difference between the 3- to 6-day and the 0- to 2-day periods of 3.75 (95% CI 1.90–7.39) [208]. However, this effect is thought to be outweighed by the benefits of rotavirus vaccination [208, 209]. Other studies did not find an increased risk of SAEs, including intussusception for Rotateq [210, 211], although post-introduction surveillance studies are required to detect rare events associated with vaccination. Post-licensing data from Mexico has already shown an association with a short-term risk of intussusception in approximately 1 of every 51,000 to 68,000 vaccinated infants [201]. However, given the rareness of the event, data from different countries may need to be pooled.
A phase I study evaluated the safety and tolerability of a human neonatal rotavirus vaccine (RV3-BB). This vaccine has been developed as a rotavirus vaccine candidate for administration at birth. The results showed that a single dose of RV3-BB vaccine was well tolerated by adults, children and infants [212], which supports the progression of RV3-BB to phase II trials.

6.1.5 Current/ongoing research

The IDS of the RIVM participates, together with 14 other countries in the European Rotavirus Network (EuroRotaNet), which was established in January 2007; the IDS joined the project in June 2008. EuroRotaNet combines the results of the participating countries into an overview of circulating serotypes of rotavirus in consecutive rotavirus seasons in Europe. The results for the Netherlands for 2012 are given in section 6.1.3.

6.1.6 International developments

Brazil was the first country to introduce rotavirus vaccination into its national immunisation programme, in 2006 [213]. Since then, countries worldwide have followed: about 20 other countries in Latin America, US, Australia and South Africa. In the European Economic Area, nine countries have included rotavirus vaccination in their national immunisation programme (Austria, Belgium, Bulgaria, Finland, Latvia, Luxembourg, Poland, Slovenia and the UK) and the Ministry for Social Affairs of Estonia recommends rotavirus vaccination without including it in the national immunisation programme so far [214]. Monovalent Rotarix and pentavalent Rotateq are oral rotavirus vaccines marketed internationally. Two other vaccines are manufactured in China (Lanzhou lamb rotavirus vaccine) and in Vietnam (Rotavin-M1), but these are not available internationally [215].

In 2012, a Cochrane systematic review of rotavirus vaccines was published [211]. The review included 29 trials with 101,671 participants testing Rotarix versus a placebo, and 12 trials with 84,592 participants testing Rotateq versus a placebo. In countries with low-mortality rates, Rotarix prevents 86% and 85% of severe rotavirus diarrhoea cases among children aged less than one year and less than two years, respectively. For Rotateq, this was estimated at 87% for children aged less than one year and 82% for children aged up to two years. No trials of the Lanzhou lamb rotavirus vaccine have been found.
In Austria, Zlamy et al. found an overall reduction of 74% in hospitalisations due to rotavirus gastroenteritis after the introduction of rotavirus vaccination in children up to 18 years of age [216]. They further explored the effect of vaccination on nosocomial rotavirus, and found a reduction of 93% in these infections. Since the introduction of the vaccination, no deaths have been recorded among the cases of nosocomial infections (2.5 years) in comparison

with three cases in the four years before vaccination was introduced. A comparable reduction in rotavirus gastroenteritis after the introduction of rotavirus vaccination has been summarised by Patel et al. [217].

In Spain, the two vaccines were banned from the market from June to November 2010 after the detection of circovirus in both vaccines [218]. This lead to a pronounced and immediate increase in hospitalisations in children under one year of age, and a subsequent decrease after the resumption of vaccination. In the 12-23 months age group, an increase was also seen which persisted despite the resumption of vaccination, as catch-up vaccination is not possible in this age group due to strict age restrictions for rotavirus vaccination.

A systematic review of the possible correlation between anti-rotavirus serum IgA antibody titer after vaccination and rotavirus vaccine efficacy was published [219]. It concluded that IgA titers may be a useful predictor of vaccine performance, as a consistent correlation was found between these titers and the efficacy of Rotarix and Rotateq. Overall, IgA titers <90 appeared to be associated with lower efficacy and to wane during the second year after vaccination. Identification of a critical titer of IgA antibody that is needed for adequate vaccine efficacy on the individual level was not possible within this review, as it was based upon group data. Although a trend in antibody levels and efficacy exists, other effectors are likely to contribute to host defence.

In Belgium, a comparison was made between data on post-vaccination rotavirus-related hospitalisations and previously modelled estimates of the effect of vaccination [220]. The observed reduction in hospitalisations exceeded the reduction predicted by the static model. Two explanations were identified. First, an indirect herd effect in children too young for vaccination and too old for vaccination when the vaccination was introduced was observed in the hospitalisation data, which was not included in the model. Second, no waning of vaccine efficacy was seen in the observed data, whereas this was assumed in the model. After exclusion of the assumed waning effect from the model, the model still underestimated the total vaccine benefit, mainly because of the herd effect. The study concluded that it is likely that previously published economic models underestimated the total benefit of rotavirus vaccination.

6.1.6.1 Cost-effectiveness

Recently, two reviews regarding the cost-effectiveness of universal rotavirus vaccination have been published. Plosker [221] has evaluated the cost-effectiveness of rotavirus vaccination in developed countries. It was not possible to state definitively whether a universal rotavirus vaccination programme was cost-effective, although the results of analyses in some countries suggested that this was the case. It was also difficult to draw conclusions regarding the cost-effectiveness of the monovalent rotavirus vaccine relative to that of the pentavalent rotavirus vaccine. Aballea et al. [222] also made a review of health economic evaluations of rotavirus vaccination. He also found remarkable variation in conclusions between studies. One of the key factors explaining such variability was the perspective used for estimating costs: analyses from a societal perspective consistently led to more favourable results than analyses from a third-party payer perspective, as savings in terms of productivity loss avoided were taken into account. Furthermore, estimates of QALYs gained were highly sensitive to the inclusion of cases without medical attention (mild cases) and utility lost by caregivers. To establish the full economic value of rotavirus

vaccination, Alballea suggested that dynamic transmission models be used to account for herd protection.

Two studies assessed the cost-effectiveness of rotavirus vaccination in the Netherlands. According to Bruijning et al. [223], rotavirus vaccination for high-risk infants with prematurity, a low birth weight or severe congenital pathology was highly cost-effective in the Netherlands. Universal vaccination was considered to be cost-effective if herd immunity was enclosed, and vaccine prices were € 60 at most. Supported by an unrestricted grant from SPMSD, Tu et al. [224] updated a cost-effectiveness analysis of rotavirus vaccination in the Netherlands published in 2011. At the assumed total vaccination cost of € 75 per child and including new hospitalisation data and herd immunity, rotavirus vaccination would be much more cost-effective than indicated in the original study. The incremental cost was only between € 3,000 and € 4,000 per QALY.

Coyle et al. [225] assessed the cost-effectiveness of infant vaccination against rotavirus in Canada. From a health care system perspective, the incremental cost per QALY gained from was $122,000 for Rotateq and $108,000 for Rotarix. Because the majority of rotavirus infections do not require emergency department visits or hospital admission, such a programme would not be considered cost effective. From a societal perspective, both vaccination strategies were considered both cost saving and more effective. Atkins et al. [226] incorporated a dynamic transmission model, including herd immunity effects, to assess the cost-effectiveness of rotavirus vaccination in England and Wales. In the base case situation, the pentavalent rotavirus vaccination was likely to be cost-effective at £60 per course (£ 27,000 per QALY). In some other scenarios, the vaccination was predicted to be not only cost-effective but also cost-saving. Rotavirus vaccination has been on the immunisation schedule for England and Wales since July 2013.

6.2 Varicella zoster virus (VZV) infection

E.A. van Lier, J.M. Kemmeren, A.W.M. Suijkerbuijk, W. Luytjes, G.A. Donker, I. Stirbu-Wagner, *P. Jochemsen, H.E. de Melker*

6.2.1 Key points

- No striking changes occurred in the VZV epidemiology in the Netherlands in 2012.
- The Integrated Primary Care Information (IPCI) databases showed that complications were recorded in 21% of the varicella cases that consulted a GP and that these complications were most often mild. Referral to secondary health care was low (2%).

6.2.2 Epidemiology

6.2.2.1 Disease

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 Dutch Sentinel General Practice Network (CMR) and the Dutch primary care database (LINH) (Table 12) [227-229]. 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 [228]. 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, LINH registration has been in use since 2002. From 1 January 2014 onwards, LINH and the Sentinel GP Network will be part of the Dutch Primary Care Database. The registration will be expanded extensively with a number of general practices but also with data from other primary care disciplines. At this moment the data for 2012 are not yet ready to be extracted.

Table 12 Incidence of GP consultations per 100,000 due to varicella or herpes zoster in 2002-2011 (rounded off to tens)

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

* Dutch Sentinel General Practice Network (CMR) [227, 228].

** Dutch primary care database (LINH) [229].

From literature it is known that periodic outbreaks of varicella occur, with an inter-epidemic cycle of two to five years [230]. In contrast, the incidence of herpes zoster is stable over time, which is consistent with the literature [231]. The incidence of GP consultations per 100,000 due to varicella is highest in the age groups below five years, whereas for herpes zoster it is highest in the age groups above 50 years (Figure 24) [227-229]. A review showed that data indicate that herpes zoster incidence is comparable (about 340 per 100,000) and increases with age with the same magnitude across Europe, especially after 50 years of age [232].

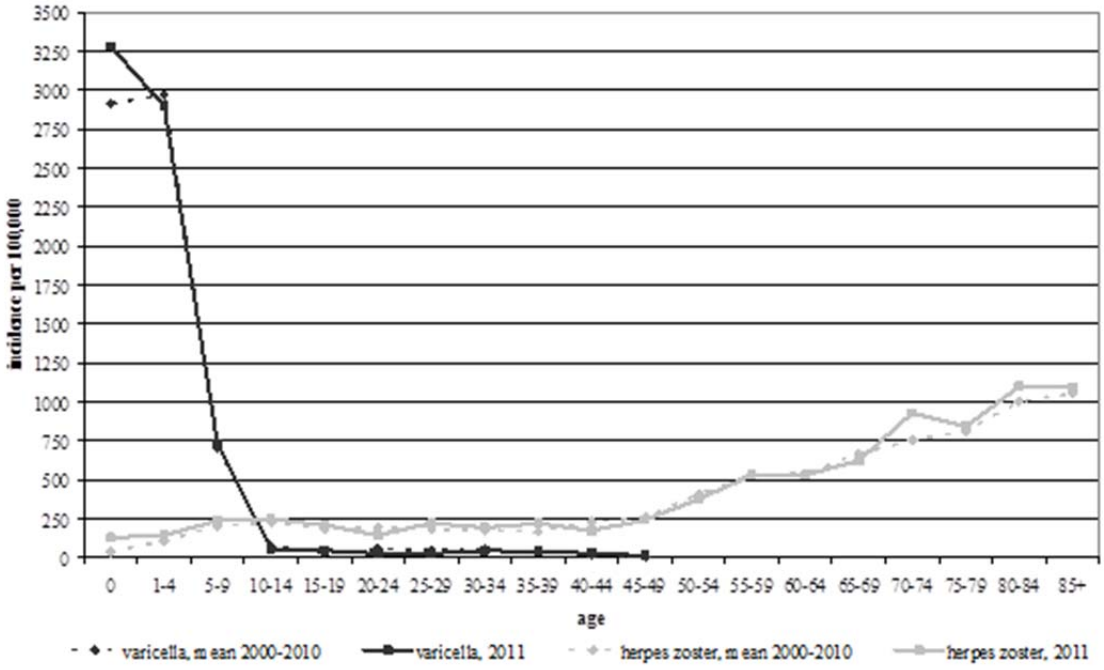


Figure 24 Incidence of GP-consultations per 100,000 for varicella and herpes zoster in 2011 versus mean incidence in 2000–2010 [227-229]

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

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 [233]; the incidence per 100,000 population is shown in Table 13. 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 reported here because some patients are admitted more than once within the same year. The incidence of hospitalised patients with herpes zoster was – like GP consultations – stable in the period 2000-2012. The incidence of hospitalised patients due to main diagnosis varicella is highest among new-borns and hospitalisations due to herpes zoster highest among the oldest age groups (Figure 25).

Table 13 Incidence per 100,000 of hospitalisations due to main and side diagnosis varicella or herpes zoster, 2002–2012 [233]

Syndrome	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Varicella – main	1.4	1.7	1.7	1.5	1.9	1.4	1.7	1.5	1.9	1.7	1.5
Varicella – main + side	2.2	2.5	2.6	2.2	2.8	2.1	2.4	2.2	2.7	2.6	2.3
Herpes zoster – main	2.7	2.2	2.5	2.2	1.9	2.0	2.0	2.4	2.1	2.2	2.1
Herpes zoster – main + side	5.1	4.9	5.0	4.3	3.9	3.9	3.8	4.5	4.5	4.6	4.4

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).

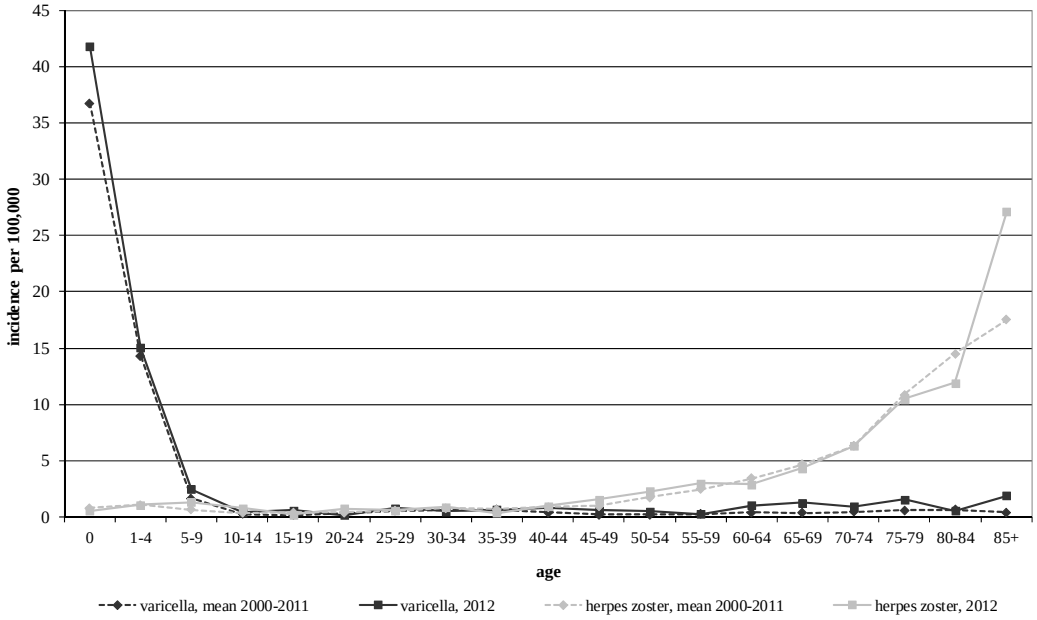


Figure 25 Incidence of hospitalised patients per 100,000 for main diagnosis varicella and herpes zoster in 2012 versus mean incidence in 2000-2011 [233].

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

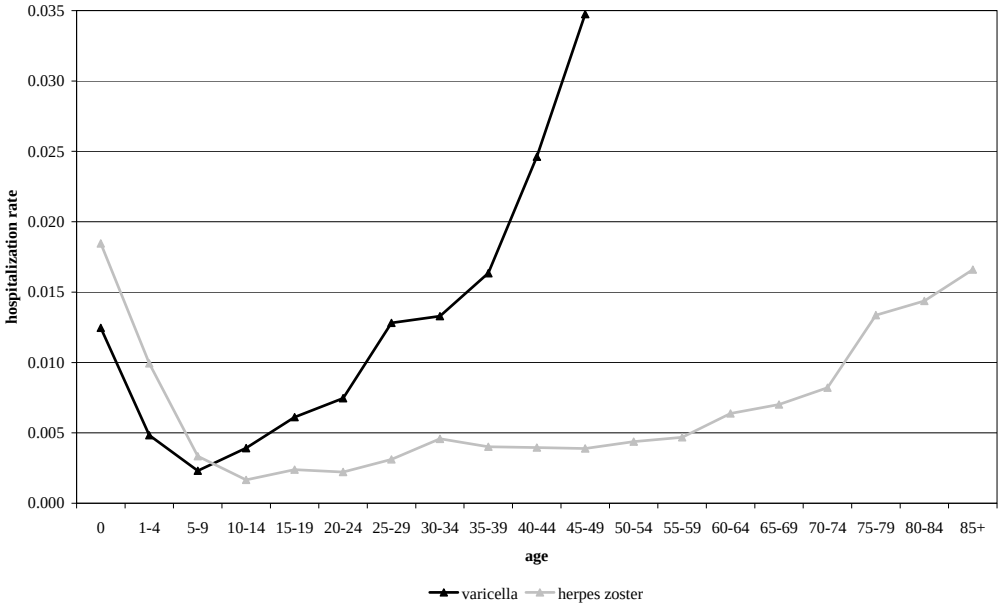


Figure 26 Mean hospitalisation rate 2000–2011 (number hospitalised patients [233]/number of GP consultations) [227-229]
Note: Varicella cases in people older than 49 are only sporadically reported by GPs and are therefore not included.

Deaths

The number of deaths due to main diagnosis varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02) was derived from CBS (Table 14) [234]. In 2012, there were two reported deaths in which the main cause was given as varicella and 21 deaths with herpes zoster as the main cause. It is known that national death certificate data greatly overestimates deaths in which herpes zoster is the underlying or contributing cause of death [235]. Mahamud et al. concluded that most deaths for which herpes zoster was determined not to be the underlying or contributing cause were people who 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 those with several diseases (herpes zoster occurs primarily among elderly peolple with multiple comorbid conditions), especially if detailed medical information is not available to the certifying physician. If we apply their rate of deaths in which herpes zoster was validated as the underlying cause of death on the Dutch population in 2012 (0.25 (range 0.10–0.38) per 1 million population before introduction of vaccination [235]), we would expect 4.2 deaths (range 1.7–6.4) instead of the 21 deaths that were reported in 2012.

Table 14 Number of deaths with main cause varicella or herpes zoster, 2002–2012 [234]

Syndrome	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Varicella	4	6	4	1	3	5	0	1	2	1	2
Herpes zoster	26	14	15	15	24	21	14	20	25	20	21

6.2.2.2 Immune surveillance

The results of the PIENTER-2 study, which confirmed the young age of VZV infection in the Netherlands already found in PIENTER-1, have been published recently [236]. An additional analysis of the PIENTER-2 data showed that the

decay rate for maternal VZV antibodies was 7.36 per year and that the duration of protection of maternal antibodies against varicella was 3.4 months for new-borns [237].

6.2.3 Pathogen

So far, the specific determinants of attenuation in VZV vaccines have been uncertain. A recent study showed that the ORF0 SNP is a likely determinant of attenuation [238].
ntroduction 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.

6.2.4 Adverse events

6.2.4.1 Varicella vaccination

In the US, the first case of fatal varicella due to vaccine-strain VZV was reported [239]. A 15-month-old girl developed a varicella-like rash 20 days after varicella vaccination that lasted for two months despite acyclovir treatment. Her failure to thrive and repeated hospitalisations early in life (starting at five months) for presumed infections and respiratory compromise treated with corticosteroids were suggestive of a primary or acquired immune deficiency. Experience of varicella vaccine indicates that SAEs are very rare and mostly occur in immunocompromised patients.
A phase III two-centre trial assessed the safety of a new, fully liquid, hexavalent DTaP-IPV-HepB-PRP-T vaccine [240]. A booster dose of this vaccine at 15–18 months of age showed it to be as safe as licensed comparators, following primary series administration with or without a hepatitis B vaccine and co-administered with MMR+V.

6.2.4.2 Herpes zoster vaccination

Several studies evaluated the safety of herpes zoster vaccination in adults. In subjects aged >= 60, a live, attenuated varicella zoster virus vaccine is generally well tolerated [241], with or without diabetes mellitus [242], even after a second dose [243]. The use of a live-attenuated zoster vaccine in immunocompromised individuals (i.e. systemic lupus erythematosus (SLE)) is still controversial. However, in a pilot study of the immunogenicity of the zoster virus in patients with SLE no serious adverse events occurred [244]. In a meta-analysis Gagliardi et al. showed that zoster vaccine is safe but that a younger age group (i.e. 60 to 69 years) experienced more adverse events [245]. However, overall zoster vaccine produces few systemic adverse events and injection site AEs of mild to moderate intensity.

A phase I study evaluated the safety and reactogenicity of an adjuvanted recombinant subunit candidate vaccine containing varicella zoster virus envelope glycoprotein E [246]. The most commonly reported local and general solicited symptoms were pain and fatigue. Back pain and chills were the most frequently reported unsolicited symptoms. There were no reports of death, SAEs, or autoimmune mediated inflammatory disorders. Therefore, this study indicated that the two-dose regimen of this vaccine exhibited a clinically acceptable safety profile in healthy adults.

6.2.5 Current/ongoing research

Insight into the disease burden of varicella in the Netherlands is essential in the decision making process as to whether or not to introduce routine childhood

varicella vaccination in the Netherlands. Last year we presented results from a study conducted within the IPCI database by Erasmus MC, Universal Medical Center. This study confirmed earlier findings of a relatively low disease burden (incidence of GP consultations and hospitalisations) due to varicella in the Netherlands compared with other countries [247].
Of all (probable) varicella cases, 81% came to the general practice for a consultation, 22% had telephone contact with the general practice, 10% went to a central GP point for a consultation (outside the normal working hours of their own GP practice) and 0.3% were visited at home by the GP.
Most patients contacted their GP just because of the typical clinical picture of varicella (fever and itching vesicles). Varicella complications were recorded in 21% of all cases. The complications most often mentioned were bacterial super infection of skin lesions (7% of all (probable) varicella cases), otitis media (5%), pharyngitis/tonsillitis (4%), conjunctivitis (2%) and gastro-enteritis (1%); neurological complications were seen in 0.5%.
Medication related to (complications of) varicella was prescribed to 54% of all cases. The most often prescribed medications were local skin medication (pruritus control and general skin care (31%)), antipyretics (11%) and antimicrobials (systemic (8%) or local (7%)).
Referral to secondary health care was low: 98% of the (probable) varicella cases were treated by the GP only, 1.1% were referred to a specialist, 0.7% contacted the emergency department of a hospital and 0.6% were admitted to an hospital.
Preliminary results from research on the willingness to vaccinate against diseases not included in the Dutch NIP showed that only 28% of Dutch parents with at least one child aged under four years had a positive intention to vaccinate their child(ren) against varicella if such a vaccination were added to the NIP. Of parents who were asked to choose between three vaccination options, 19% preferred two varicella vaccinations, 30% one varicella vaccination (resulting in protection against severe varicella but a significant probability of mild symptoms of varicella) and 51% no varicella vaccination. The main reason why parents do not want their child to be vaccinated against varicella is that they see varicella as a mild disease against which vaccination is not necessary. According to a significant proportion of the parents (36%), replacement of the MMR vaccination with an MMRV vaccination without freedom of choice is a (very) bad idea; on the other hand 28% think this a (very) good idea. The knowledge of parents regarding varicella zoster virus is limited on some points (among others the relationship between varicella and herpes zoster and the extent of healthcare utilisation due to varicella).
In 2013, 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. Guzzetta et al. proposed a mathematical model of VZV transmission and the development of herpes zoster that includes the biological hypothesis of 'progressive immunity' as first proposed by Hope-Simpson [248]. According to this hypothesis, cell-mediated protection against herpes zoster increases after each episode of exposure to VZV.
In addition, experience with different vaccination schedules, both in clinical trials and after introduction in the national immunisation programmes of different countries, is under evaluation to achieve the most effective vaccination schedule for the NIP. This information will be used in cost-effectiveness analysis.

6.2.6 International developments

In Australia, where vaccination against varicella was introduced in 2005, a reduction of almost 70% in hospital admissions related to varicella was found in the period 2007–2010 compared with the period 1999–2001, with a vaccination

coverage above 80% at two years of age [249]. In Navarre (Spain), where universal varicella vaccination was introduced in 2007, the incidence of varicella decreased by 97% and the incidence of hospitalisations for varicella by 89% (2012 compared with 2006) [250]. Results from the Bavarian Varicella Surveillance Project (BaVariPro), a regional surveillance project in Munich (Germany), showed that since the introduction of routine varicella vaccination in 2004, coveragehas reached 68% while paediatric varicella cases have decreased by 67% and paediatric hospitalisations by 43% [251].
Since the article by Goldman & King [252] no new data with regard to the possible effect of universal varicella vaccination on herpes zoster incidence have become available. Goldman & King concluded that universal varicella vaccination has not proven to be cost-effective in the US, partly because proponents have failed to consider an increase in herpes zoster in adults. A multi-country model of VZV transmission and reactivation by Poletti et al. suggested that an increase in the incidence of herpes zoster after varicella vaccination is not certain [253]. Since there is still a lot of uncertainty, the possible effect of universal varicella vaccination on the incidence of herpes zoster remains a point of interest.

Recently, three reviews and three European economic evaluations have been published regarding universal childhood varicella vaccination and herpes zoster vaccination for the elderly. Unim et al. reviewed the economic burden of varicella disease and the benefit of universal varicella vaccination in different settings, pending its implementation in all Italian regions [254]. They included 23 economic evaluations in this review and found that the studies were favourable to the introduction of universal varicella vaccination, being cost saving and having a positive impact on morbidity. Varicella vaccination could save the country between € 637,762 (infant strategy) and € 53 million (combined infant and adolescent strategy) annually. Bilcke et al. assessed the cost-effectiveness of a universal childhood varicella zoster vaccination programme in Belgium, using the most recent Belgian data on the varicella zoster burden [255]. Furthermore, they investigated the possible additional benefit of zoster booster vaccination for adults at 50 or 60 years of age. If exogenous natural boosting exists, a net loss in QALYs is expected for several decades after implementing a universal chickenpox vaccination programme, due to an increase in zoster mainly in people aged 50-80 years. Therefore, it is currently unclear whether implementing a universal VZV vaccination programme in Belgium would be cost-effective. If decision-makers decide to implement a childhood vaccination programme, closely monitoring zoster incidence for at least a decade is essential. In addition, decision-makers could consider combining such a programme with the vaccination of older adults against zoster. Szucs et al. summarised the literature available on the cost-effectiveness of herpes zoster vaccination in a systematic review [256]. They identified and included 11 economic evaluations. Most studies evaluated the cost-effectiveness of universal herpes zoster vaccination in adults aged 50 years or 60 years and older. All but one of the studies concluded that most vaccination scenarios are cost-effective and that the vaccination of specific subgroups such as the older age group would be most cost-effective. Drolet et al. summarised the evidence regarding the burden of illness, efficacy, safety and cost-effectiveness of herpes zoster vaccination in developed countries, to assist evidence-based policy making [257]. They found that the overall burden of illness associated with herpes zoster and post herpetic neuralgic pain is substantial. Second, the safety and efficacy of the zoster vaccine in reducing the burden of disease have been clearly demonstrated in large clinical controlled trials. Uncertainty remains, however, about the vaccine's duration of protection. They concluded that vaccination against herpes zoster is likely to be cost-effective if the vaccine is

given at approximately 65 years of age and if vaccination generates protection longer than ten years. Bresse et al. assessed the cost-effectiveness of vaccination against herpes zoster and postherpetic neuralgia in France, using a published Markov model [258]. The cost-effectiveness of vaccinating individuals aged over 65 years or between 70 and 79 years was evaluated over their lifetime, from a third-party payer perspective. French-specific data were combined with results from clinical studies and quality-of-life-based utilities from the literature. Herpes zoster vaccination proved to be highly cost-effective in both populations. ICER's were estimated at between € 9,513 and € 12,304 per QALY gained. De Boer et al. evaluated vaccination of the elderly against herpes zoster versus no such vaccination in the Netherlands and found less cost-effective results than the French study [259]. Vaccination against herpes zoster might be considered cost-effective for ages ranging from 60 to 75 years if a threshold of € 50,000 per QALY gained were used; at € 20,000 per QALY this might not be the case. Although the results of this study are difficult to compare with a previous Dutch study on the cost-effectiveness of vaccination against herpes zoster [260], both studies concluded that with regard to the optimum age for vaccination, the lowest ICER can be achieved with vaccination at 70 years of age (marginally cost-effective at a threshold of €20,000 per QALY gained).
The results of these economic evaluations are highly sensitive to assumptions on vaccine efficacy, duration of protection, epidemiological data (incidence of herpes zoster) and vaccine price.

6.3 Hepatitis A

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

6.3.1 Key points

- In 2012, the number of hepatitis A infections (121 cases) remained low compared with previous years.
- Forty percent of the Dutch cases were reported to be travel-related, mostly among people who had visited Morocco.

6.3.2 Epidemiology

In 2012, 121 cases of hepatitis A were reported in the Netherlands corresponding to 0.7 cases per 100,000 inhabitants. This was similar to 2011 (125 cases) and the lowest number since hepatitis A became notifiable in 1999 (Figure 27 / Appendix 1). Almost one in four reported cases (23%) was hospitalised, slightly higher than in 2010–2011 (20%) and higher than in the years 2003-2009 (8-18%). The mean age of patients hospitalised with a hepatitis A infection was 39 years (range 3–83 years, 18% aged <19 years) compared with 23 years of age (range 2–78 years, 57% 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, all in adults.

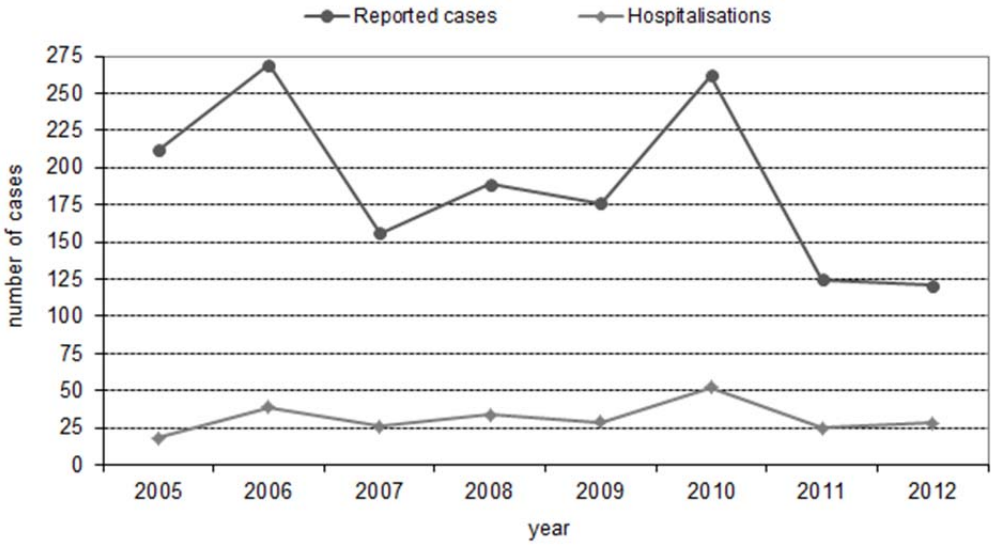


Figure 27 Number of reported and hospitalised cases of hepatitis A, 2005-2012

The percentage of travel-related cases was lower in 2012 (40%) than in previous years (43-54%), except 2010, when 31% of the cases reported were travel-related. Half of the travel-related cases (24/48) had been to Morocco; other countries were reported for a maximum of three times. Twenty clusters including a total of 59 of the 121 cases could be deduced from the reports: 13 clusters were at least partly travel-related, mostly to Morocco (7 clusters); in seven clusters no relation with travel was found. The largest outbreak contained 11 reported cases and was situated around a primary school. Overall, for one-third of the cases the most likely source of infection was contact with another infected person. About a quarter of the cases reported food or water, mostly consumed abroad, as the source of the infection. Part of these cases was found due to a cluster investigation after an identical strain was found in four cases; mussels were the most likely source of the infection.

6.3.3 *Pathogen*

IgM-positive samples can be sent to the IDS 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 taken. This is often preferred for young children who are not ill but may be related to a cluster. In 2012, a total of 147 serum and faecal samples were tested, of which 76 (52%) were positive and 72 (95%) also could be typed, resulting in 36 unique sequences in 13 clusters of 2 to 9 cases. No great differences were seen in the genotype prevalences in comparison with 2011. However, several remarkable molecular clusters were identified, requiring further investigation. In 2012, four such clusters occurred that were further investigated by the Municipal Health Service (GGD), food safety authority and RIVM. Three clusters of cases were traced back to a suspected common food-related source in. One of them was the investigation leading to mussels as the most likely source (see section 6.3.2).

6.3.4 *Adverse events*

In a retrospective cohort study it was shown that local reactions to hepatitis A vaccines are relatively uncommon, and that the choice of arm versus thigh injections has no effect on risk of such events [261]. Studies from China reported no differences in safety levels among domestic live attenuated hepatitis A vaccine, domestic inactivated hepatitis A vaccine and imported inactivated

hepatitis A vaccine under routing or emergency vaccination [262, 263]. This confirms results from post marketing surveillance, which has shown that domestic preservative-free inactivated hepatitis A vaccine has a good safety profile [264].

6.3.5 *Current/ongoing research*

Initially, the typing of IgM-positive samples by the IDS was done for a period of two years but it is now to be continued for an indefinite period 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 the event of a cluster of cases, where the dates of illness onset lie close together, a cluster investigation is usually started to ascertain the cause.

6.3.6 *International developments*

A group of HIV-infected children (n=80) and children receiving immunosuppressive medication for treatment of rheumatic diseases (n=80) in the Netherlands were vaccinated with a combined hepatitis A (HAV) and B (HBV) vaccine (Ambirix®) [265]. Immune responses after the first dose were low: 55–71% (HAV) and 17–27% (HBV). These responses increased after the second dose to 99–100% for HAV and 93–97% for HBV. When vaccinating these groups because of forthcoming travel or post-exposure prophylactic treatment for HAV, one should keep the low immune response for HAV after the first dose in these groups in mind.
The kinetics of maternally acquired anti-HAV were investigated in infants from Nicaragua [266]. In Nicaragua, HAV is highly endemic. For these infants, seroprevalence was 100% in the cord blood. Seroprevalence was still 100% at two and seven months of age, but antibody levels had declined sharply. The half-life of maternal antibodies was estimated at 40.2 days (95% CI: 38–43 days). The median protection duration was calculated to be 11.1 months, with the loss of maternal protection by the age of 13.2 months for 95% of the children.

6.4 Meningococcal serogroup B disease

L. Mollema, M.J. Knol, P. Kaaijk, N.Y. Rots, J.M. Kemmeren, A.W.M. Suijkerbuijk, H.E. de Melker, G.A.M. Berbers, A. van der Ende

6.4.1 *Key points*

- The incidence of meningococcal B disease among one-year-olds and less increased in 2012, whereas the total number of MenB cases was comparable to 2011. In 2013 (until July), a small increase in MenB disease was observed.
- The proportion of the dominant PorA genosubtype P1.7-2,4 in serogroup B isolates decreased from 2000 to 2012. Until 2011, a decrease in the dominant FetA type F1-5 was also observed, with an increase again in 2012.
- In January 2013, the European Commission approved the meningococcal B vaccine Bexsero (Novartis) for use in individuals from two months of age.
- On the basis of cost-effectiveness the Joint Committee on Vaccination and Immunisation (JCVI) has recommended not to implement the 4CMenB (Bexsero) vaccine in the national immunisation programme of the UK.

6.4.2 *Epidemiology*

From 2001 to 2011 the number of patients with meningococcal B disease had been decreasing, as can be seen in Figure 28 and Table 15. In 2012, the total number of MenB cases was comparable with 2011; however, the incidence among less than 12-month-olds and one-year olds increased from 7.6 to 8.9 per 100,000 and from 5.4 to 7.6 per 100,000, respectively. Three MenB cases died, two girls of less than 12 months old and two years old and one man of 76 years old. In 2013 (until July), a small increase in MenB cases was observed compared with the previous two years. Eighty per cent of all meningococcal cases concerned MenB and 54% of MenB disease concerned children younger than five years in 2012.

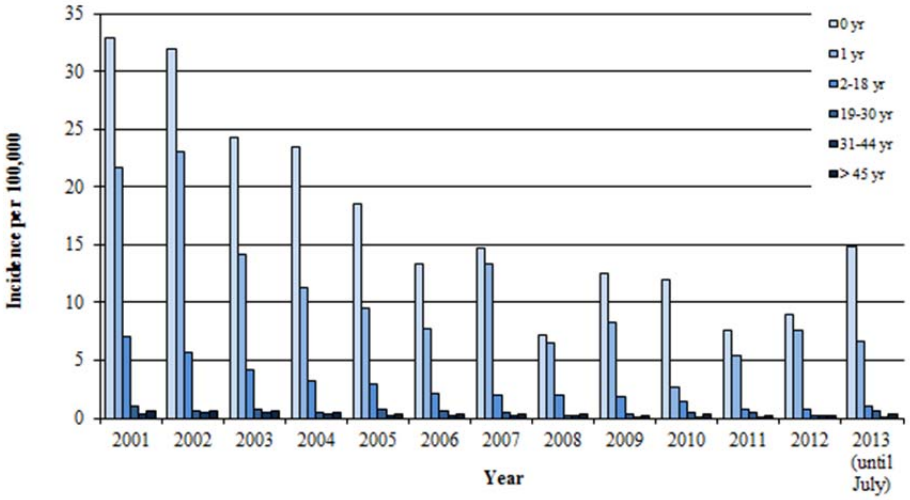


Figure 28 Age-specific incidence of MenB disease, 2001–2013 (until July)

Table 15 Absolute number of patients with MenB disease per age-category from 2001–2013** (**until July)*

Age in yrs	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013**
0 yr	68	65	49	47	36	25	27	13	23	22	14	16	13
1 yr	44	48	29	23	19	15	25	12	15	5	10	14	6
2-18 yr	235	191	142	108	102	74	69	67	62	48	24	24	16
19-30 yr	25	15	17	11	19	14	11	5	9	12	11	6	7
31-44 yr	14	16	18	10	7	7	5	5	2	4	1	5	1
> 45 yr	36	40	38	32	26	20	22	26	15	21	15	11	12
Total	*422*	*375*	*293*	*231*	*209*	*155*	*159*	*128*	*126*	*112*	*75*	*76*	*55*

*Numbers may differ from the 2012 report as a different date variable was used.

6.4.3 *Pathogen*

The proportion of the dominant PorA genosubtype P1.7-2,4 decreased from 40% of all serogroup B isolates in 2000 to 9.2% in 2012. Until 2011, a decrease in the dominant FetA type F1-5 had also been observed in the serogroup B isolates. This FetA type is strongly linked with PorA VR1/VR2 P1.7-2,4 and the MLST clonal complex ST41/44. In 2012, this FetA type increased again, but associated with diverse PorA subtypes, accounting for 35% of group B meningococci.

6.4.4 *Vaccines*

Recently, the first MenB vaccine was licensed in Europe (January 2013) and Australia (August 2013) for individuals aged two months or older. This vaccine, 4CMenB (Bexsero from Novartis), contains three recombinant proteins, and outer membrane vesicles (OMV) derived from MenB.
The licensed 4CMenB schedule for infants is a three-dose series at 2–5 months of age, with an interval ≥1 month, followed by a booster dose at 12–23 months. For children aged between 6 and 11 months and children aged between 12 and 23 months the schedule is two primary doses with a booster dose in the second year of life. For children aged between 2 and 10 years and adolescents from 11 years of age and adults (no data in adults above 50 years of age) the schedule is two primary doses without the need for a booster dose.
The 4CMenB vaccine contains subvariant 1.1 of factor H binding protein (fHbp), which is present in strains causing 12.3% (of 1,052 European strains collected from July 2007 to June 2008) of invasive disease in five European countries (England and Wales; France; Germany; Norway; and Italy). Antibodies produced against fHbp by infants appear to be specific to the sub-variant, and expression of this protein varies up to tenfold within the different MenB strains. The second component, Neisserial adhesion A (NadA), is present in 22.3%. The third component of 4CMenB is Neisserial heparin binding antigen (NHBA; variant 2), which is found in 24.7% of European isolates. It is uncertain whether antibodies in human infants are cross-protective between different variants. The frequency of PorA P1.4, the fourth component of Bexsero as a vesicle, in European isolates was 20.2%.
A method of predicting vaccine coverage of 4CMenB, known as the Meningococcal Antigen Typing System (MATS) has been developed and produced by the manufacturer of 4CMenB (Novartis) and is described by Donnelly et al. [267]. Predicted vaccine coverage for at least one antigen was 78% for the European strains(of 1052 European strains collected from July 2007 to June 2008), varying from 73% (England and Wales) to 87% (Italy).
Because 4CMenB vaccine is not based on the polysaccharide capsule, *N. meningitides* strains belonging to any serogroup may express antigens present in the vaccine.
Other MenB vaccines under development are the bivalent recombinant lipoprotein 2086 vaccine [268, 269] and vaccines based on OMV, such as the nonavalent PorA vaccine with intrinsic adjuvating activity due to presence of less toxic (lpxL1) lipopolysaccharide (LPS) [270].

6.4.5 *Safety and immunogenicity*

The safety of 4CMenB vaccine in infants was assessed in a primary and booster phase III trial [271]. This trial showed that reactogenicity was in general acceptable. However, the vaccine was associated with more solicited systemic AEs (particularly fever) in infants when co-administered with other, routine, infant vaccines than when these vaccines were administered alone.
Fever (≥38-38.5°C) rates of up to 80% were reported in the infant groups, especially when 4CMenB was given concomitantly with routine vaccines. Evidence suggests that the rise in body temperature induced by the vaccine can be tempered by prophylactic use (at 0, 4–6 and 12 hours after vaccination) of paracetamol without affecting the immunogenicity [272].

Clinical trials of 4CMenB in infancy have shown that one month after a three-dose infant series of 4CMenB at 2, 4 and 6 months or 2, 3 and 4 months, SBA titers of ≥ 1:5 are achieved for strain 44/76-SL in 99.2–100%, 5/99 in 99.2–100% and NZ98/254 in 79-86.1% of infants. Intriguingly, after immunisation at 2 and 4 months in the early phase II infant study, 95%, 100% and 74% of

participants had SBA titers ≥ 1:4 for these strains respectively. These data suggest that adequate immunogenicity may be achieved by a two-dose infant priming schedule followed by a booster dose at 12 months of age, which is further assessed in another study.
Waning of antibodies is observed after 40 months in children who were immunised in infancy and received a booster dose at 12 months of age. Further studies are ongoing to evaluate the persistence of immune response in this age group and the immunogenicity and reactogenicity of a preschool booster.

In general, good SBA titers were found against the selected MenB reference strains and no influence of clinical relevance was observed regarding immune response to routine infant vaccines when coadministered. The potential of 4CMenB to protect against wild-type circulation strains should be proven after implementation of the vaccine in routine schemes.

6.4.6 Cost-effectiveness

Previously, implementation of a MenB vaccine in routine vaccination schemes was estimated to be cost-effective [273]. However, since then, MenB disease incidence has declined drastically in the Netherlands. Therefore, Pouwels et al. [274] re-assessed the potential cost-effectiveness ratio of vaccinating infants in the Netherlands with MenB vaccine. He found that routine infant vaccination in a four-dose schedule could prevent 39 cases of MenB disease in a single birth cohort, corresponding to a total gain of 133 QALYs. However, this strategy is unlikely to be cost-effective at vaccine costs of €40 per dose (€ 243,778 per QALY). If the MenB disease incidence increases or the vaccine price falls substantially below € 40, routine infant vaccination has the potential to be cost-effective.
Christensen et al. [275] also evaluated the cost-effectiveness of a MenB vaccination and estimated the potential impact of introducing such a vaccine in England. They estimated that 27% of meningococcal disease cases could be prevented over the lifetime of an English birth cohort by vaccinating infants at 2, 3, 4 and 12 months of age with a vaccine that prevents disease only; this strategy could be cost-effective at £ 9 per vaccine dose. Substantial reductions in disease (71%) could be produced after ten years by routinely vaccinating infants in combination with a large-scale catch-up campaign, using a vaccine which protects against carriage as well as disease; this could be cost-effective at £ 17 per vaccine dose. In conclusion, according to the authors, new 'MenB' vaccines could substantially reduce disease in England and be cost-effective if competitively priced, particularly if the vaccines can prevent carriage as well as disease.

A follow-up of the study by Christensen et al. [275] was performed to take into account advice from the meningococcal sub-committee of the Joint Committee on Vaccination and Immunisation (JCVI) in the UK. This independent study, which was not published, was conducted by the University of Bristol and London School of Hygiene and Tropical Medicine [276]. This study investigated the impact and cost-effectiveness of routine infant and/or adolescent immunisation programmes, using Bexsero®, with and without catch-up campaigns and a routine toddler immunisation programme. The study suggested that, assuming a high efficacy against three-quarters of meningococcal strains in the UK, routine infant immunisation would prevent directly around a quarter of cases over the lifetime of each single vaccinated birth cohort. Furthermore, the study suggested that routine immunisation of infants and adolescents would reduce directly and indirectly the annual number of cases by a total of more than one-third to one-half in around ten years depending on the assumptions made about vaccine

efficacy against the acquisition of meningococcal carriage. However, based on the accepted threshold for cost-effectiveness used in the UK and the results of a wide range of sensitivity analyses, routine infant immunisation on its own or combined with adolescent immunisation is highly unlikely to be cost-effective at any vaccine price.

6.4.7 Current/ongoing research

See section 5.9.7.

6.4.8 International developments

In June 2013, the JCVI made an interim statement on the use of Bexsero® meningococcal B vaccine in the UK. The JCVI concluded that, on the basis of the available evidence, routine infant or toddler immunisation using Bexsero® was highly unlikely to be cost-effective at any vaccine price (based on the accepted threshold for cost-effectiveness used in the UK) and could thereforenot be recommended. Similarly, if the vaccine had little or no impact on the acquisition of meningococcal carriage, adolescent immunisation was highly unlikely to be cost-effective at any vaccine price. However, the efficacy of the vaccine against meningococcal carriage is highly uncertain and under some scenarios routine adolescent immunisation might be cost effective. However, current evidence is insufficient to support a recommendation for the introduction of a routine adolescent immunisation programme using Bexsero®.
The JCVI further noted that a population-based evaluation of Bexsero® in adolescents is required as well as an evaluation of acceptability and the safety profile in infants. The infrastructure and expertise available in the UK would make the UK an ideal setting for such an evaluation.
Based on clinical data, the JCVI also considered the selective vaccination of certain groups and concluded that once Bexsero® was available it should be offered selectively to the same groups at high risk of IMD that are currently offered meningococcal ACWY conjugate vaccine. Bexsero® could also be offered to laboratory workers who are at high risk of occupational exposure to meningococcal serogroup B.
Last, the JCVI supports plans for Public Health England to produce guidance on the use of Bexsero® for close contacts of cases in outbreaks of IMD associated with meningococcal serogroup B.

Studies evaluating the presence of the 4CMenB antigens in oropharyngeal carriage isolates have been conducted but the results have not yet been published in detail. Preliminary data from a randomised controlled trial in which UK university students received two doses of 4CMenB suggest a modest decrease (16.5%; 95% CI 1.5–29.2) in *N. meningitides* carriage in the year following immunisation [277].

A clinical trial of numerous formulations of a meningococcal 'ABCYW' vaccine, in which recombinant meningococcal proteins were combined with the conjugate quadrivalent serogroup A,C, W and Y vaccine, was completed in adolescents in 2011 [277].

6.5 Meningococcal non-serogroup B and C types

L. Mollema, M.J. Knol, P. Kaaijk, N.Y. Rots, J.M. Kemmeren, A.W.M. Suijerbuijk, H.E. de Melker, G.A.M. Berbers, A. van der Ende

6.5.1 *Key points*

- In 2012, of 95 meningococcal cases, 16 were non-serogroup B and C.
- After a decrease in incidence of meningococcal serotype Y disease in 2012, an increase was observed in 2013 (until July).

6.5.2 *Epidemiology*

Since 2001, the number of patients with meningococcal serotype W (MenW) disease had decreased to 3–7 cases each year, except in 2011, with only one case. One woman of 84 years old has died in 2012 from MenW disease.
After a small decrease in 2012, an increase in 2013 (until July) in meningococcal serotype Y (MenY) cases was observed, higher than in 2010 or 2011. This increase was mostly among individuals aged 45 years or older. One woman of 51 years of age died in 2012 from MenY disease. The number of cases caused by serotype Y and W remained relatively low. One MenZ case was reported in 2012. Furthermore, no MenA/E29/X/Z cases were reported in 2012 or 2013 (until July).

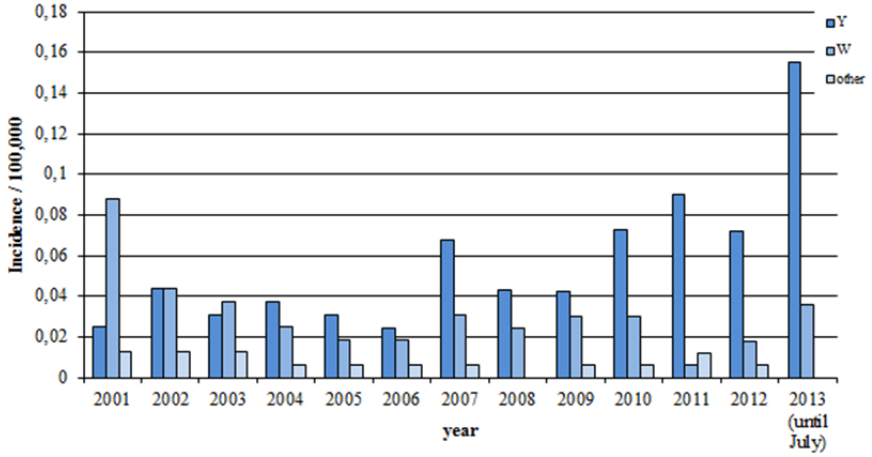


Figure 29 Incidence of Meningococcal non-B and non-C types (e.g. A, 29E, W, X, Y, Z), 2001-2013 (until July)

Table 16 Absolute number of patients with MenW disease per age category, 2001-2013** (**until July)*

Age in yrs	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013**
0 yr	3	1	0	0	1	0	1	0	0	0	0	0	1
1 yr	0	0	3	0	0	1	1	1	1	1	0	0	0
2-18 yr	3	2	1	0	1	1	1	0	1	2	1	0	1
19-30 yr	3	0	0	0	0	0	0	1	0	0	0	1	0
31-44 yr	1	1	0	0	0	1	1	0	1	0	0	1	0
> 45 yr	4	3	2	4	1	0	1	2	2	2	0	1	1
Total	*14*	*7*	*6*	*4*	*3*	*3*	*5*	*4*	*5*	*5*	*1*	*3*	*3*

*Numbers may differ from the 2012 report as a different date variable was used.

Table 17 Absolute number of patients with MenY disease per age category, 2001-2013** (**until July)*

Age in yrs	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013**
0 yr	0	0	1	0	0	0	0	0	0	0	0	0	1
1 yr	0	0	0	0	0	0	0	0	0	1	0	0	1
2-18 yr	0	1	1	3	0	0	1	0	1	2	5	5	2
19-30 yr	1	2	0	0	0	0	2	0	1	2	2	1	0
31-44 yr	0	0	1	0	0	0	0	1	0	2	2	1	0
> 45 yr	3	4	2	3	5	4	8	6	5	5	6	5	9
Total	*4*	*7*	*5*	*6*	*5*	*4*	*11*	*7*	*7*	*12*	*15*	*12*	*13*

*Numbers may differ from the 2012 report as a different date variable was used.

6.5.3 Pathogen

There are no indications that the properties or the composition of the population structure of non-serogroup B and C types changed.

6.5.4 Adverse events

See section 5.9.5.

6.5.5 Cost-effectiveness

See section 5.9.6.

6.5.6 Current/ongoing research

See section 5.9.7.

6.5.7 International developments

In the UK no increase in MenY IMD has been observed any more, but rather an increase in the MenW 2a strain. In Scandinavia, an increase in MenY IMD was again observed. In Sweden, one clone might be responsible for the increase in MenY IMD, though not in 2012, when no specific clone was found [55].

7 Other possible future NIP candidates

N.Y. Rots, P. Kaaijk, A.W.M. Suijkerbuijk, W. Luytjes

The aim of this chapter is to update information with regard to vaccines for infectious diseases in development that have reached the clinical testing phase and are relevant for the Netherlands. An overview of vaccines currently under development is given in Table 18, where underlined vaccines are at the clinical testing phase. Relevant developments of combination vaccines are described in earlier chapters.

Table 18 Summary of vaccines currently under development

Bacterial diseases	Viral diseases	Parasitic diseases	Therapeutic treatments
Buruli ulcera	CMV	Fascioliasis[a]	Allergic rhinitis
Clostridium difficile	Dengue fever[a]	Human African Trypanosomiasis[a]	Alzheimer's
Chlamydia	Ebola	Hookworm	Breast cancer
Escherichia coli	Epstein–Barr	Leishmaniasis[a]	Cervical cancer
Helicobacter pylori	Genital herpes	Lymphatic filariasis[a]	Cocaine addiction
Leprosya	Hepatitis C	Malaria	Colorectal cancer
Plague	Hepatitis E	Onchocerciasis (river blindness)[a]	Lung cancer
Pseudomonas aeruginosa	Herpes simplex	Schistosomiasis[a]	Melanoma
Shigella	HIV	Hookworm[a]	Multiple sclerosis
Staphylococcus	Influenza		Nicotine addiction
Streptococcus group A & B	Parainfluenza		Pediatric tumors
Trachoma[a]	RSV		
Tuberculosis	SARS		
	West Nile		

[a] Neglected tropical diseases

Source: WHO/IFPMA/BVGH/PhRMA

7.1 Respiratory syncytial virus (RSV)

Respiratory syncytial virus (RSV) is the major cause of lower respiratory tract infections (LRI) in infants worldwide. In addition, people with heart/lung disease or an immunodeficiency disorder, and the elderly are at increased risk of severe LRI upon RSV infection. The 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. This equals to 2.78 per 100,000 infants under 12 months of age; in the elderly, this number is estimated to be much higher, i.e. 120 per 100,000 [38].

Although there is at present no licensed RSV vaccine available, it is a priority target for several vaccine developers. Over the last two decades, several RSV vaccine concepts have been tested in (early) clinical trials with published results. These include live attenuated vaccines for intranasal application, i.e. a cold-passaged, temperature-sensitive (*cpts*) RSV vaccine concept, and a live recombinant viral (chimeric) vector vaccine against RSV (F-protein) and parainfluenza (MEDI-534). In addition, various subunit RSV vaccines (with and without aluminium-containing adjuvant) intended for intramuscular administration have been developed and some have been tested clinically with

published data. However, at present none of the vaccine concepts has entered advanced stages of clinical development. Therefore, introduction of these vaccines to the market is not expected within the next five years. When an RSV vaccine becomes available, several vaccination strategies may come under consideration. Maternal immunisation with a RSV vaccine seems a feasible approach that may be effective in protecting infants during the most vulnerable period against severe LRI. Therefore, this vaccination strategy deserves more attention. Although immunisation of young infants might also be promising, it needs to be determined whether the presence of maternal antibodies will interfere with the induction of an adequate immune response. Apart from infants, other groups at high risk of severe RSV disease, have been identified. Since these risk groups seem to overlap significantly with those at risk for severe influenza and pneumococcal disease, simultaneous vaccinations against these infectious diseases could be considered for these groups. The seasonality of these diseases also overlaps significantly [278].

7.2 Tuberculosis

Tuberculosis (TB) is the world's second leading cause of death and morbidity. More than 2 billion people, equal to one-third of the world's population, are infected with TB bacilli, the microbes that cause TB. In the Netherlands, 1,003 and 958 TB cases were reported in 2011 and 2012, respectively [279]. A growing concern is the steady increase in the number of TB cases that are resistant to most of the medications in use.

The only TB vaccine used in the world today was developed in the 1920s. Although BCG is effective in protecting infants against childhood forms of the disease, its protection of adolescents and adults is suboptimal. New TB vaccines are urgently needed because of the apparent lack of effect of the BCG vaccine on rates of adult contagious pulmonary tuberculosis and the risk of disseminated BCG disease in immunocompromised individuals coupled with the emergence of drug-resistant strains of *Mycobacterium tuberculosis*. New vaccine concepts are under development, including modification of the existing vaccine, BCG, as well as development of modern platforms such as recombinant proteins, novel adjuvants, recombinant viruses, and DNA [280]. These concepts may elicit a more appropriate immune response or direct the response against more suitable targets for the control or prevention of TB. Progress toward the development of TB vaccines has however been disappointing. The most advanced clinical candidate vaccine is the MVA85A vaccine, which was first developed at Oxford University. This vaccine is an attenuated modified vaccinia Ankara (MVA) which expresses the *M. tuberculosis* (Mtb) antigen (Ag) 85A and was found to be safe and immunogenic in humans, generating T cell responses to the encoded Ag85A. This candidate entered a phase II efficacy trial with 2,797 infants in 2009. However, results from this phase II study recently published in the Lancet showed poor efficacy of this vaccine against tuberculosis (17%) and against *M. tuberculosis* infection (-3.8%) [281]. Another recent disappointment was the vaccine candidate AERAS-422, a recombinant BCG vaccine that overexpressed three Mtb antigens (Ag85A, Ag85B and Rv3407). While AERAS-422 was found to be safe and immunogenic in animal models, further clinical development has been stopped as a consequence of a safety signal; administration at high dose to young adults was followed 60 or more days later by shingles in some individuals [280]. GSK has developed a vaccine against tuberculosis, Mtb72F/AS02A, which is currently being tested in a phase II trial. Mtb72F is a recombinant protein comprising two antigens (Mtb39a and Mtb32a), which are expressed in *M.*

tuberculosis and in BCG but not in other mycobacteria. AS02A is a GSK proprietary Adjuvant System inducing humoral responses and type 1 T cell responses [282].

7.3 HIV/ AIDS

Up to 2013, a cumulative total of 19,985 HIV-infected people were registered in the Netherlands, including those who died and patients lost to follow-up. On average, about 1,100 new cases are diagnosed each year, of which 700–750 are men who have sex with men (MSM). The number of new diagnoses therefore remains more or less stable, despite the increasingly early start of treatment. In about half of HIV patients in the Netherlands, the virus is successfully suppressed with combination antiretroviral therapy [283].

An investigational ALVAC-HIV (canary Pox) vaccine developed by Sanofi Pasteur was shown to be safe and modestly effective in preventing HIV infection but did not protect those at highest risk of HIV. In-depth analysis of the results of this trial showed a 60% vaccine efficacy in the first year, which fell to 31% by the end of the six-year trial. Based on these results, a new collaboration, called the Pox-Protein-Public Private Partnership (P5: U.S. National Institute of Allergy and Infectious Diseases/Division of AIDS, Bill & Melinda Gates Foundation, HIV Vaccine Trials Network, U.S. Military HIV Research Program, Sanofi Pasteur, Novartis Vaccines and Diagnostics, South African Medical Research Council), has been established to substantiate and extend the clinical results obtained with this vaccine. GSK is testing a prophylactic recombinant HIV vaccine in a phase I trial, and the vaccine is also being tested for HIV disease immunotherapy in a phase II trial.

7.4 Hepatitis C

In the Netherlands in 2012, the number of registered acute hepatitis C virus (HCV) infections was 50, compared with 78 in 2011. The number of positive samples as determined by virological laboratories in the Netherlands was 874 in 2012 compared with 1134 in 2011 [284]. Although one might argue that HBV is much more infectious and prevalent than HCV, HCV infection has a higher chronicity and worse disease progression than HBV infection. A vaccine that prevents and treats HCV infection is therefore desirable. Despite major advances in the understanding and treatment of hepatitis C, a preventive vaccine is not yet in sight. The marked genetic diversity and multiple mechanisms of persistence of hepatitis C virus, combined with the relatively poor immune response of the infected host against the virus, are major barriers.

Two candidates have advanced to clinical trials based on promising results in chimpanzees [285]. One of these vaccine candidates contains recombinant envelope glycoproteins E1 and E2 of HCV-1 and is formulated with a potent adjuvant, MF59. In a phase 1 study of human volunteers, it induced strong antibody responses with strong HCV-1 neutralising capacity and to a lesser extent genotype 2 virus. However, further development of this candidate vaccine is currently on hold. The other candidate is a T cell-based vaccine, based on two serologically distinct adenoviral vectors: a rare human adenovirus, Ad6, and a chimpanzee adenovirus, Ad3Ch3. Both vaccines induced strong cellular responses that targeted multiple regions and were sustained for up to one year. Neutralising antibodies and T cell responses against the adenovirus were also detected after the priming and probably limited the boosting effect of a second

immunisation. To overcome this problem, a different viral vector, MVA, is currently being tested on about 300 intravenous drug users in a prime-boost regimen with the AdCh3 vector in a phase I/II study to assess safety, efficacy and immunogenicity.

7.5 *Clostridium difficile*

The *Clostridium difficile* bacterium (CD) can be found in 80% of all infants and 9% of all adults but rarely causes infections in healthy people. However, it is a significant threat to patients with disruption of their intestinal flora by antibiotics, especially in healthcare settings, or with immunocompromising conditions. In hospitals it is one of the leading causes of infectious diarrhoea in adults, particularly the elderly. There is currently no vaccine available. It is estimated that more than 2700 hospitalised patients annually will develop CD infections (CDI) of which 100 will succumb attributable or contributable to CDI. In these estimations, the impact of CDI in healthcare facilities other than hospitals was not included. Therefore, the true number of patients with CDI admitted to healthcare facilities will be higher [38].

Sanofi Pasteur has developed a toxoid-based candidate vaccine (ACAM-CDIFF) against *C. difficile* for which a clinical phase III programme has just started that will include up to 15,000 adults at 200 sites across 17 countries. Volunteers should be aged 50 or older and be preparing for hospitalisation or have had at least two hospital stays and have received systemic antibiotics in the past year [286].

7.6 *Staphylococcus aureus*

Staphylococcus aureus is a bacterium that commonly colonises human skin and mucosa (e.g. inside the nose) without causing any problems. Staphylococcus infections, including methicillin-resistant *Staphylococcus aureus* (MRSA), occur most frequently among vulnerable people in hospitals and healthcare facilities (such as nursing homes and dialysis centres). In the Netherlands, the incidence of MRSA in hospitals is 1% and in the general population it is 0.13%, which is low compared with other EU countries. The Netherlands, Norway and Sweden have the lowest MRSA-prevalence in Europe [38].

Several companies (Sanofi Pasteur together with Intercell; Pfizer; Novartis; GSK) are developing a prophylactic vaccine against *Staphylococcus aureus*. Vaccination prior to surgery might be a feasible strategy. Several of these vaccines are currently being tested in phase I-III trials. However, it will be at least five years before these vaccines are available for the market.

7.7 *Pseudomonas aeruginosa*

The majority of 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 on account of their resistance to antibiotics. No incidence figures are available for the Netherlands.
A vaccine (IC43) developed by Intercell/Novartis 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. Currently, a phase II/III study has been initiated to investigate the immunogenicity and safety of the recombinant pseudomonas vaccine, IC43, in 800 intensive care patients.

7.8 Group B streptococcus

Infection with Group B streptococcus (GBS) can cause serious illness and sometimes death, especially in new-borns, the elderly, and people with a compromised immune system. In the Netherlands, around 20% of all pregnant women carry GBS. It is estimated that 50% of the children of these carrying mothers are colonised after birth. Approximately 1% of these children develop an infection. The mortality rate among these infected children is 5 per 100 [38]. The overall incidence of neonatal GBS-sepsis is estimated to be between 0.4 and 1.9 per 1000 live births. It also occasionally results in maternal death by causing upper genital tract infection, which progresses to septicaemia.

Novartis is currently initiating a phase II clinical trial with a trivalent conjugate vaccine against GBS. The study will investigate the immune response in healthy pregnant women. In addition, the study will investigate the amount of vaccine-induced antibodies, which are transferred to the newborn.

7.9 Cytomegalovirus

Cytomegalovirus (CMV) infects the majority of the global population and rarely leads to severe acute clinical symptoms. In contrast, CMV is a leading infectious cause of congenital disease and a common cause of severe complications in transplant recipients. The overall prevalence of congenital CMV infection in the developed world is estimated at 0.6%. Approximately 10% of congenitally infected infants have signs and symptoms of disease at birth, and these symptomatic infants have a substantial risk of subsequent neurologic sequelae. An effective preconceptual vaccine against CMV could protect against long-term neurologic sequelae and other disabilities.
The RIVM, in collaboration with Leiden University Medical Centre (LUMC), is currently performing a study on the disease burden and risk factors of congenital CMV infections in the Netherlands (Crocus study) [287].

Four recent CMV vaccine candidates with published clinical data have been reviewed: a subunit, a DNA, a peptide vaccine and a vaccine consisting of alphavirus replicon particles [288]. These vaccines are in early clinical development and are likely to be targeted at adolescent females prior to their first pregnancy and/or to patients prior to organ or cell transplantation. Dempsey et al. assessed the cost-effectiveness of CMV vaccination on an adolescent female group in the US [289]. They found that universal vaccination of adolescent females to protect their future children against congenital CMV infection is likely to be cost-effective if CMV vaccines achieve at least a 61% reduction in the incidence of CMV disease in neonates.

7.10 Norovirus

In the Netherlands each year approximately 4.5 million people suffer from stomach flu. Almost half a million of these cases are caused by noroviruses (RIVM). Ligocyte Pharmaceuticals [290] is developing a bivalent virus-like particle (VLP) norovirus vaccine adjuvanted with monophosphoryl lipid A (MPL) and aluminium 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 that a norovirus vaccine will have to be reformulated frequently, perhaps yearly, as is the case for influenza seasonal vaccine.
Bartsch et al. developed a simulation model of a human norovirus vaccine for the US to determine such vaccines' potential economic value [291]. According to the model, vaccination would prevent 100–6125 norovirus gastroenteritis cases per 10,000 vaccinees. Low vaccine cost (≤$ 50) resulted in cost savings and a more expensive vaccine led to costs per case averted comparable to other vaccines. In the US, vaccination could avert approximately 1.0–2.2 million cases (efficacy 50%, 12 month duration), costing an additional $ 400 million to $ 1 billion, but could save ≤$ 2.1 billion (48 month duration). Bartsch et al. suggested that children under the age of five years are the most attractive target population in terms of both cases averted (between 11% and 41% of all vaccines with a 50% efficacious vaccine) and costs. People aged 65 years and older may be the next most favourable group to vaccinate, since they disproportionately suffer severe, and therefore experience more health care costs.

7.11 *Borrelia burgdorferi*

Lyme borreliosis is a zoonotic disease caused by the *Borrelia burgdorferi sensu lato* bacterium transmitted to humans by the bite of an *Ixodes* spp. tick (deer tick). Despite improvements in diagnostic tests and public awareness of Lyme disease, reported cases have increased over the past. In a large population study in 2006–2007, it was estimated that 1.1 million people in the Netherlands had a tick bite. General practitioners saw about 93,000 persons for tick bites and approximately 22,000 people suffered from the first symptoms of Lyme disease (erythema migrans, producing a red ring around the bite) [292]. In 2012, tekenradar.nl was initiated by RIVM as a geographical presentation in order to gain insight into how often, where and under what circumstances a tick bite or erythema migrans leads to (severe) Lyme disease. In addition, the intention of tekenradar.nl was to make people aware of the potential risks of ticks and Lyme disease.

Limitations and failed public acceptance of a human vaccine, comprising the outer surface A (OspA) lipoprotein of *B. burgdorferi* led to its demise, yet current research has reopened doors to new strategies for protection against Lyme disease. Recently, the safety and immunogenicity of adjuvanted and non-adjuvanted vaccines containing epitopes from OspA derived from *Borrelia* species was investigated in healthy adults. Results of this study with 300 participants showed that the novel multivalent OspA vaccine could be an effective intervention for the prevention of Lyme borreliosis [293]. Larger studies are needed to confirm this.

7.12 Others

Vaccines in the clinical testing phase but currently not relevant for the Netherlands due to low disease incidence are vaccines against dengue, malaria, Japanese encephalitis and West Nile virus. In the event of increased incidence these vaccines will be evaluated for introduction into the NIP.

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List of abbreviations

4CMenB	multicomponent meningococcal B vaccine
Ab	antibody
ACIP	Advisory Committee on Immunisation Practices
AE	adverse event
AEFI	adverse events following immunisation
AFP	acute flaccid paralysis
Ag	antigen
AIDS	acquired immune deficiency syndrome
AlOH	Aluminum Hydroxide
AMC	Academic Medical Centre of Amsterdam
anyHPV	any human papillomavirus types
AOM	acute otitis media
aP	acellular pertussis
a-VDPV	ambiguous vaccine-derived Polio viruses
BAO	Managerial Integration Meeting (‘bestuurlijk afstemmings overleg’)
BCG	Bacille Calmette Guérin
BES	Bonaire, Sint Eustatius and Saba, the Dutch Caribbean
bp	base pair
CB	child welfare centre
CBS	Statistics Netherlands
CCMO	Central Committee on research involving human subjects
CD	*Clostridium difficile*
CDC	Centres for Disease Control and Prevention
CDI	*Clostridium difficile* infections
cGMP	current Good Manufacturing Practices
CI	confidence interval
CIb	Centre for Infectious Disease Control
CMR	Continuous Morbidity Registration
CMV	Cytomegalovirus
cpts	cold-passaged, temperature sensitive
CSF	cerebrospinal fluid
CVP	childhood vaccine providers
CWC	child welfare centres
DNA	desoxyribo nucleïnic acid
DTP	combination of diphtheria, tetanus, and pertussis vaccines
ECDC	European Centre for Disease Control and Prevention
ED	emergency department
EMA	European Medicines Agency
EMRs	electronic medical records
EU	European Union
EV	Enterovirus
FHA	Filamentous haemagglutinin
fHbp	factor H binding protein
GBS	Group B Streptococcus
GGD	Municipal Health Service
GMC	geometric mean IgG concentrations

GMT	geometric mean titers
GP	General Practitioner
GSK	Glaxo Smith Kline
HAV	hepatitis A virus
HAVANA	Study of HPV prevalence among young girls
HBsAg	hepatitis B surface antigen
HBeAg	hepatitis B e antigen
HBIG	hepatitis B immunoglobulin
HBV	hepatitis B virus
HC	Health Council
HCV	hepatitis C virus
HepB	hepatitis B virus
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HPA	Health Protection Agency
HPV	human papillomavirus
HPV2	bivalent HPV vaccine
HPV4	quadrivalent HPV vaccine
hrHPV	high-risk human papillomavirus types
ICD	International Classification of Diseases
ICER	Incremental cost effectiveness ratio
ICPC	International Classification of Primary Care
Ig	Immunoglobulin
IPCI	Integrated Primary Care Information
IBD	invasivasive bacterial disease
IDS	Centre for Infectious Disease Research, Diagnostics and Screening
IHD	invasive *Heamophilus influenzae* type b disease
IMD	invasive meningococcal disease
IPD	invasive pneumococcal disease
IPV	inactivated polio vaccine
IR	incidence rates
ITP	immune thrombocytopenic purpura
i-VDPV	VDPVs that can be attributed to an immuno-compromised person
JCVI	Joint Committee on Vaccination and Immunisation
JIA	juvenile idiopathic arthritis
JIM	Juvenile Immunisation with Meningococcal vaccine
LINH	the Netherlands Information Network of General Practice
LMR	National Medical Registration
LPS	lipopolysaccharide
lrHPV	low-risk human papillomavirus types
LRI	lower respiratory tract infections
LUMC	Leiden University Medical Centre
MATS	meningococcal antigen typing system
MCC	meningococcal C conjugate
MenACWY-CRM	quadrivalent meningococcal CMR conjugate vaccine
MenACWY-D	quadrivalent meningococcal diphtheria toxoid conjugate vaccine
MenACWY-PS	multivalent polysaccharide meningococcal 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
MenZ	Meningococcal serogroup Z
MHS	Municipal Health Service (GGD)
MMR	combination of measles, mumps, and rubella vaccines
MMRV	combination of measles, mumps, rubella, and Varicella vaccines
MPL	monophosphoryl lipid A
MRR	mortality rate ratio
MRSA	Methicilline-resistant *Staphylococcus aureus*
MSM	men who have sex with men
Mtb	*Mycobacterium tuberculosis*
MVA	modified vaccinia Ankara
NadA	Neisserial adhesion A
NHBA	neisserial heparin binding antigen
NIP	national immunisation programme
NIVEL	Netherlands Institute for Health Services Research
NKR	the Netherlands Cancer Registry
NNV	number needed to vaccinate
NPG	National Influenza Prevention Programme
NRBM	Netherlands Reference laboratory for Bacterial Meningitis
NTHi	nontypable Hi strains
NVI	Netherlands Vaccine Institute
NVKP	foundation for critical vaccinating
OMT	outbreak management team
OMV	outer membrane vesicle
OspA	outer surface A
OPV	oral polio vaccine
PASSYON	PApillomavirus Surveillance among STI clinic Youngsters
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PEP	post-exposure prophylaxis
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
PS	polysaccharide
PspA	pneumococcal surface protein A
PWID	people who inject drugs
P5	Pox-Protein-Public Private Partnership
QALY	quality-adjusted life year
QC	quality control

RIVM	National Institute for Public Health and the Environment, the Netherlands
RNA	ribonucleic acid
RR	Relative risk
RRV-TV	oral rhesus/rhesus-human reassortant rotavirus tetravalent vaccine
RSV	respiratory syncytial virus
RV3-BB	Rotavirus vaccine
SAE	serious adverse event
SBA	serum bactericidal antibody
SIA	supplementary immunisation activity
SLE	Systemic lupus erythematodes
SNP	single-nucleotide polymorphism
STI	sexually transmitted infections
TB	tuberculosis
Tdap	tetanus, diphtheria and pertussis vaccine
TIM	Tweede Immunisatie Meningokokken C
T-PEP	tetanus post-exposure prophylaxis
UVG	under-vaccinated groups
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
WP	work package
WPV	wild poliomyelitis virus
ZonMW	The Netherlands Organisation for Health Research and Development

Appendix 1 Mortality and morbidity figures 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 (retrieved at 30-09-2013)

Data on notifications were retrieved from:
http://rivm.nl/Onderwerpen/Ziekten_Aandoeningen (retrieved at 30-09-2013)

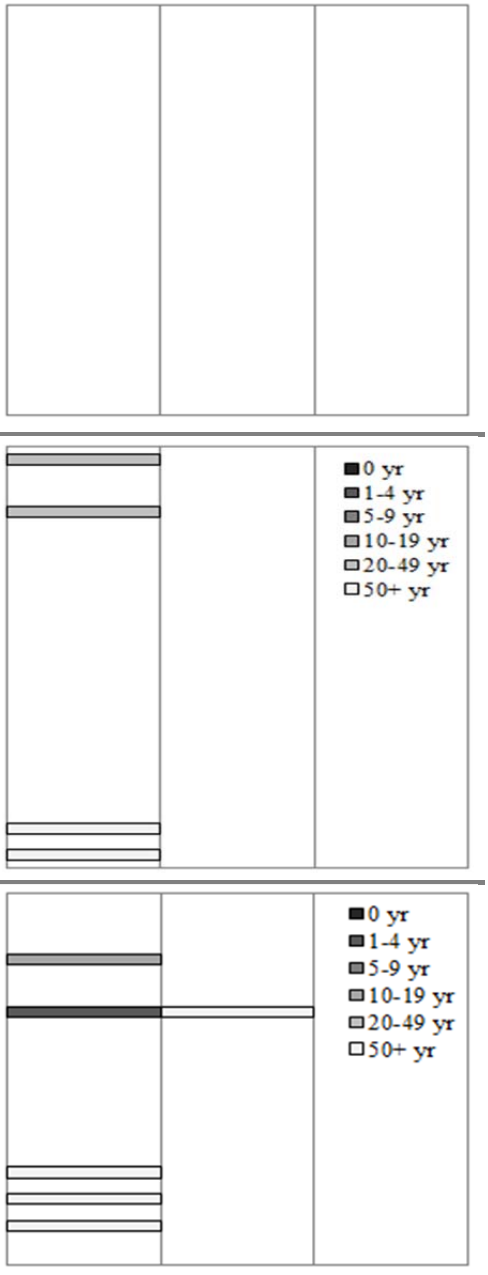
Data on hospitalisations were retrieved from the National Medical Registration (LMR). Only main diagnoses were included. Multiple hospitalisations of the same patient in the same year were excluded. For rotavirus an estimation of the hospital admissions was made with the use of the ICD9 codes 86-93 and 5589.

Data on isolates of *Haemophilus influenzae* serotype b and meningococcal and pneumococcal disease were retrieved from the Netherlands Reference laboratory for Bacterial Meningitis (NRBM). The laboratory diagnoses of the other diseases discussed in this report are data from virological laboratories of the Dutch Working Group for Clinical Virology.

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

		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Mortality	1997	0	0	0	0	0	0	0
	1998	0	0	0	0	0	0	0
	1999	0	0	0	0	0	0	0
	2000	0	0	0	0	0	0	0
	2001	0	0	0	0	0	0	0
	2002	0	0	0	0	0	0	0
	2003	0	0	0	0	0	0	0
	2004	0	0	0	0	0	0	0
	2005	0	0	0	0	0	0	0
	2006	0	0	0	0	0	0	0
	2007	0	0	0	0	0	0	0
	2008	0	0	0	0	0	0	0
	2009	0	0	0	0	0	0	0
	2010	0	0	0	0	0	0	0
	2011	0	0	0	0	0	0	0
	2012	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
	2012	0	0	0	0	0	0	0

N

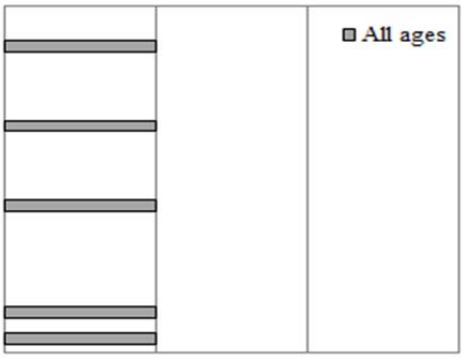


Diphtheria **ICD9 032** **ICD10 A36**

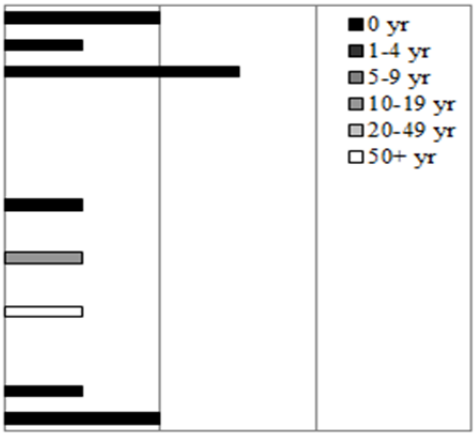
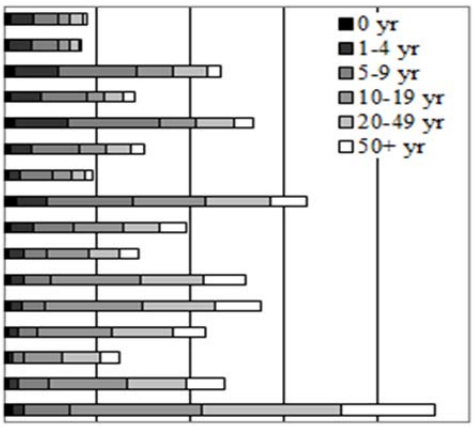
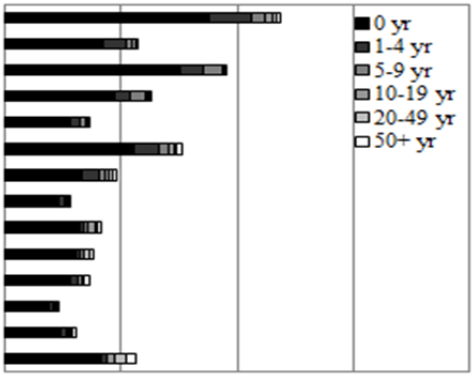
	Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
2000	0	0	0	0	0	0	0
2001	0	0	0	0	0	1	1
2002	0	0	0	0	0	0	0
2003	0	0	0	0	0	0	0
2004	-	-	-	-	-	-	1
2005	0	0	0	0	0	0	0
2006	0	0	0	0	0	0	0
2007	0	0	0	0	1	0	1
2008	0	0	0	0	0	0	0
2009	0	0	0	0	0	0	0
2010	0	0	0	0	0	0	0
2011	0	0	0	0	0	1	1
2012	0	0	0	0	0	1	1

Laboratory diagnoses

N



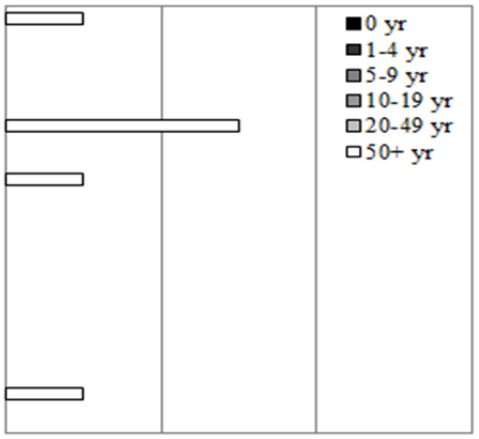
Pertussis **ICD9 033** **ICD10 A37**

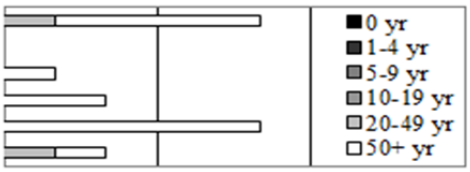
		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total	N
Mortality	1997	2	0	0	0	0	0	2	
	1998	1	0	0	0	0	0	1	
	1999	3	0	0	0	0	0	3	
	2000	0	0	0	0	0	0	0	
	2001	0	0	0	0	0	0	0	
	2002	0	0	0	0	0	0	0	
	2003	0	0	0	0	0	0	0	
	2004	1	0	0	0	0	0	1	
	2005	0	0	0	0	0	0	0	
	2006	0	0	0	1	0	0	1	
	2007	0	0	0	0	0	0	0	
	2008	0	0	0	0	0	1	1	
	2009	0	0	0	0	0	0	0	
	2010	0	0	0	0	0	0	0	
	2011	1	0	0	0	0	0	1	
	2012	2	0	0	0	0	0	2	
Notifications	1997	213	705	821	379	420	126	2,664	
	1998	134	714	921	316	310	108	2,503	
	1999	307	1,447	2,526	1,153	1,084	447	6,964	
	2000	211	976	1,460	564	648	363	4,222	
	2001	343	1,676	3,011	1,169	1,207	587	7,993	
	2002	198	666	1,540	856	810	417	4,487	
	2003	126	372	1,085	557	464	243	2,847	
	2004	363	1,007	2,745	2,387	2,091	1,133	9,726	
	2005	183	783	1,286	1,567	1,207	842	5,868	
	2006	141	469	785	1,353	981	622	4,351	
	2007	189	450	842	2,882	2,056	1,327	7,746	
	2008	194	345	776	3,128	2,325	1,477	8,245	
	2009	162	262	650	2,400	1,964	1,061	6,499	
	2010	113	165	345	1,266	1,189	637	3,715	
	2011	159	277	1,003	2,491	1,965	1,216	7,111	
	2012	235	382	1,521	4,210	4,495	3,004	13,847	
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	
	2012	166	10	1	12	20	16	226	

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
	2012	0	0	0	0	0	0	0
Notifications	1997	0	0	0	0	1	4	5
	1998	0	0	0	0	0	0	0
	2009	0	0	0	0	0	1	1
	2010	0	0	0	0	0	2	2
	2011	0	0	0	0	0	5	5
	2012	0	0	0	0	1	1	2

N

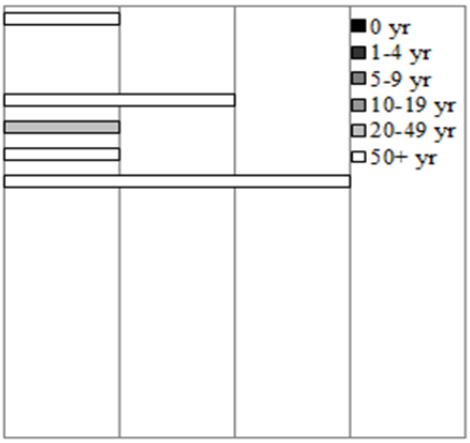




Poliomyelitis **ICD9 045** **ICD10 A80**

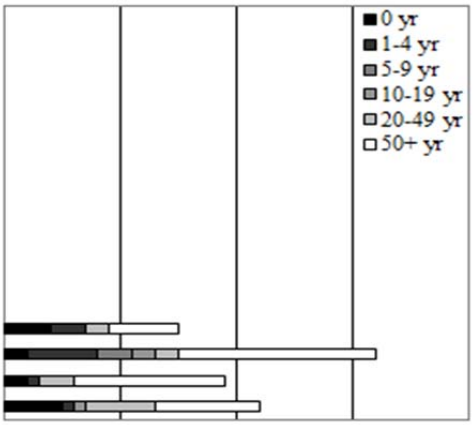
		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Mortality (Acute)	1997	0	0	0	0	0	1	1
	1998	0	0	0	0	0	0	0
	1999	0	0	0	0	0	0	0
	2000	0	0	0	0	0	2	2
	2001	0	0	0	0	1	0	1
	2002	0	0	0	0	0	1	1
	2003	0	0	0	0	0	3	3
	2004	0	0	0	0	0	0	0
	2005	0	0	0	0	0	0	0
	2006	0	0	0	0	0	0	0
	2007	0	0	0	0	0	0	0
	2008	0	0	0	0	0	0	0
	2009	0	0	0	0	0	0	0
	2010	0	0	0	0	0	0	0
	2011	0	0	0	0	0	0	0
	2012	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
	2012	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
	2012	0	0	0	0	0	0	0

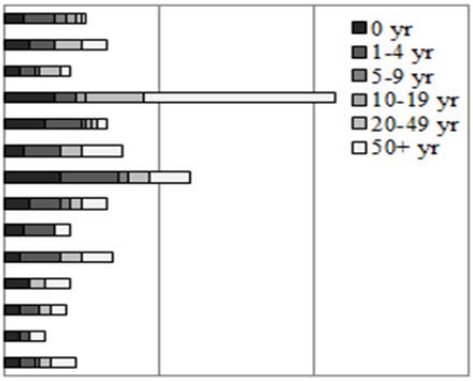
N

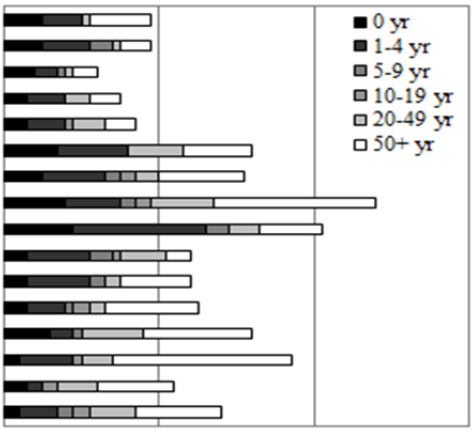


Hib **ICD9 3200** **ICD10 A41.5 G00.0**

		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total	N
Notifications*	1997	-	-	-	-	-	-	-	
	1998	-	-	-	-	-	-	-	
	1999	-	-	-	-	-	-	-	
	2000	-	-	-	-	-	-	-	
	2001	-	-	-	-	-	-	-	
	2002	-	-	-	-	-	-	-	
	2003	-	-	-	-	-	-	-	
	2004	-	-	-	-	-	-	-	
	2005	-	-	-	-	-	-	-	
	2006	-	-	-	-	-	-	-	
	2007	-	-	-	-	-	-	-	
	2008	-	-	-	-	-	-	-	
	2009	4	3	0	0	2	6	15	
	2010	2	6	3	2	2	17	32	
	2011	2	1	0	0	3	13	19	
	2012	5	1	0	1	3	9	22	
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	
	2012	3	3	1	0	2	5	14	
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	7	9	32	
	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	5	10	22	
	2012	2	5	2	2	6	11	28	





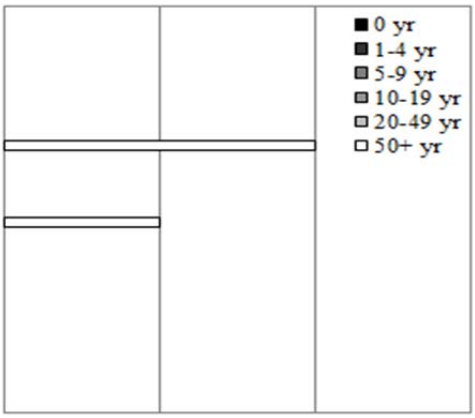


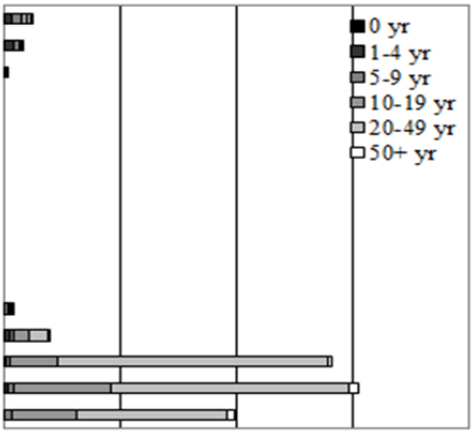
*Notifiable since 2009.
**For one patient the age is unknown.

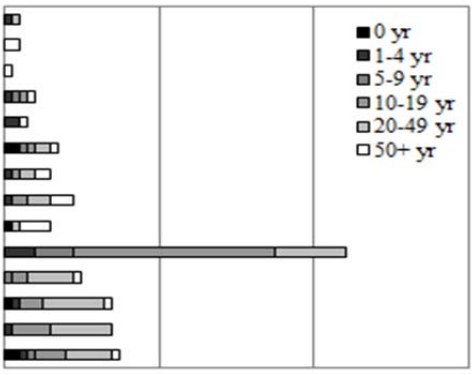
Mumps **ICD9 072** **ICD10 B26**

		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
	2012	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
	2012	0	2	12	110	260	13	397
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
	2012	2	1	1	4	6	1	16

N





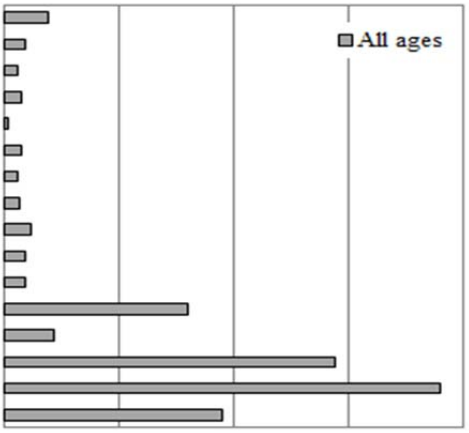


*No notifications between 1 April 1999 and 31 December 2008.

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

		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Laboratory diagnoses	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
	2012	-	-	-	-	-	-	95

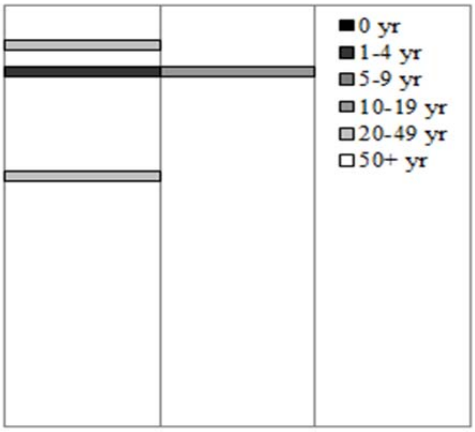
N

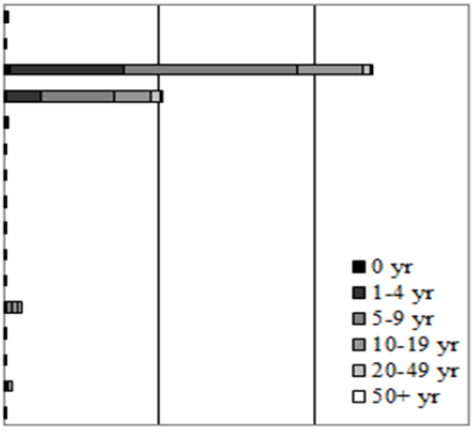


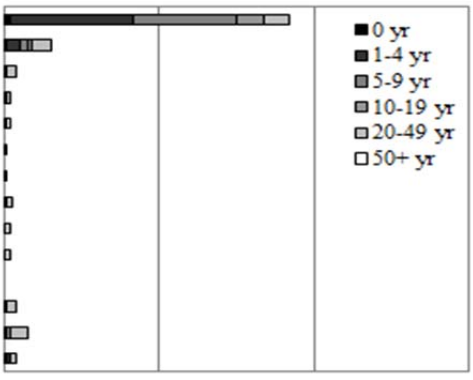
Measles **ICD9 055** **ICD10 B05**

		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
	2012	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	1,112	427	44	6	2,368
	2000	19	225	469	237	64	5	1,019
	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
	2012	1	2	0	1	6	0	10
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
	2012	1	1	0	0	2	0	4

N

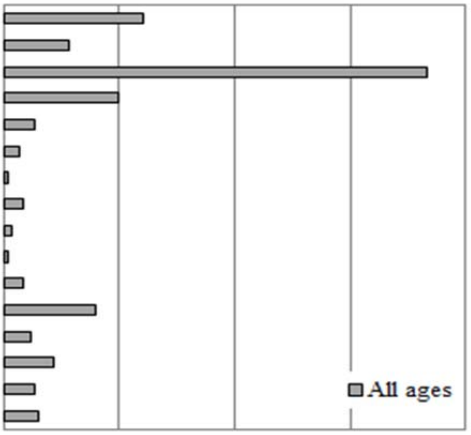




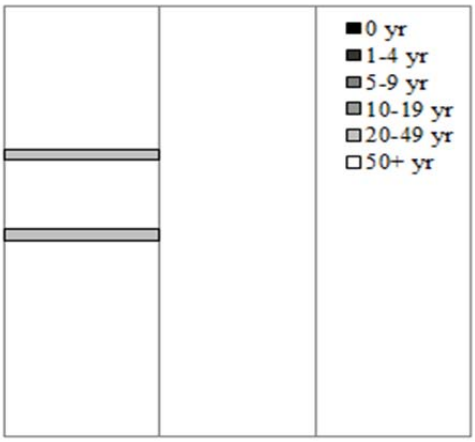
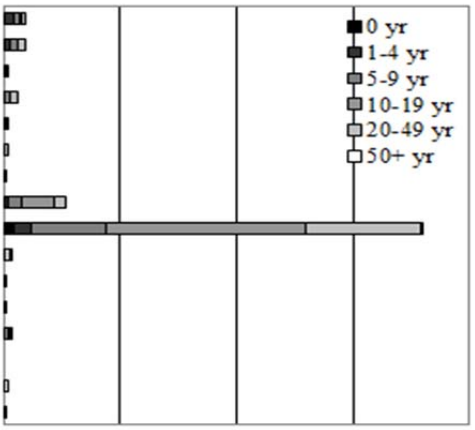
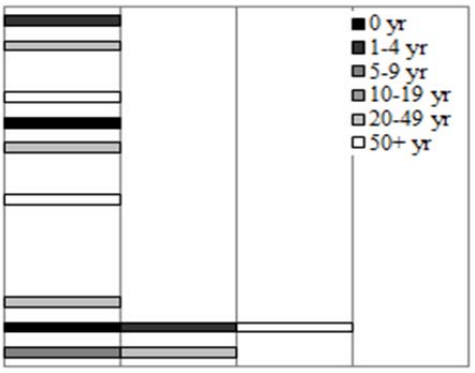


Measles **ICD9 055** **ICD10 B05**

	Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Laboratory diagnoses 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
2012	-	-	-	-	-	-	9



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

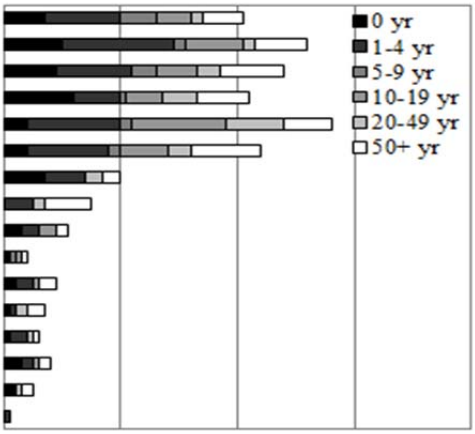
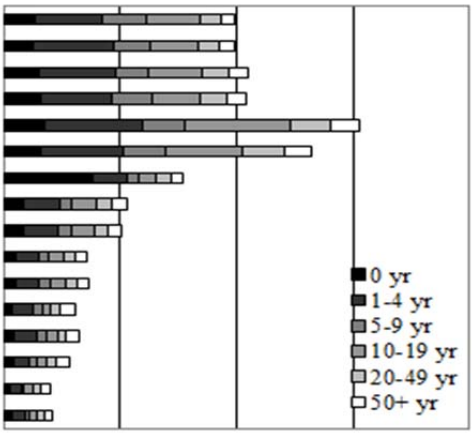
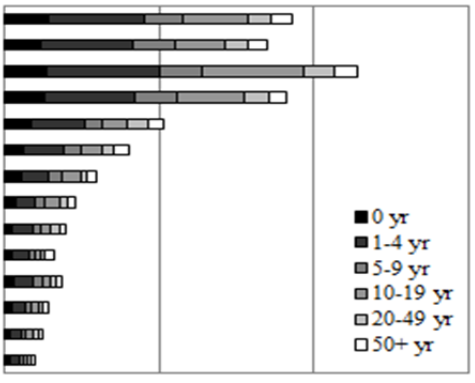
		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total	N
Mortality	1997	0	0	0	0	0	0	0	
	1998	0	0	0	0	0	0	0	
	1999	0	0	0	0	0	0	0	
	2000	0	0	0	0	0	0	0	
	2001	0	0	0	0	0	0	0	
	2002	0	0	0	0	1	0	1	
	2003	0	0	0	0	0	0	0	
	2004	0	0	0	0	0	0	0	
	2005	0	0	0	0	1	0	1	
	2006	0	0	0	0	0	0	0	
	2007	0	0	0	0	0	0	0	
	2008	0	0	0	0	0	0	0	
	2009	0	0	0	0	0	0	0	
	2010	0	0	0	0	0	0	0	
	2011	0	0	0	0	0	0	0	
	2012	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	
	2012	0	0	0	0	1	0	1	
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	
	2012	0	0	1	0	1	0	2	

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

		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Laboratory diagnoses	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
	2012	-	-	-	-	-	-	15

N

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	
	2012	0	1	0	0	0	0	1	
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	14	21	22	28	141	
	2011	13	25	4	19	20	18	99	
	2012	18	30	7	15	17	16	103	
Hospitalisation (036.0, 036.2-3)*	1999	113	251	97	167	62	52	745	
	2000	97	>234	110	129	61	48	682	
	2001	112	291	109	261	77	59	917	
	2002	106	233	108	174	65	41	742	
	2003	71	138	44	63	56	41	416	
	2004	52	102	46	55	28	41	325	
	2005	45	70	37	45	17	24	240	
	2006	31	48	26	40	19	19	185	
	2007	23	55	19	22	24	15	158	
	2008	20	46	15	13	10	28	132	
	2009	27	47	24	24	14	12	149	
	2010	20	38	12	18	11	18	118	
	2011	18	26	10	20	13	9	98	
	2012	15	26	12	10	9	10	82	

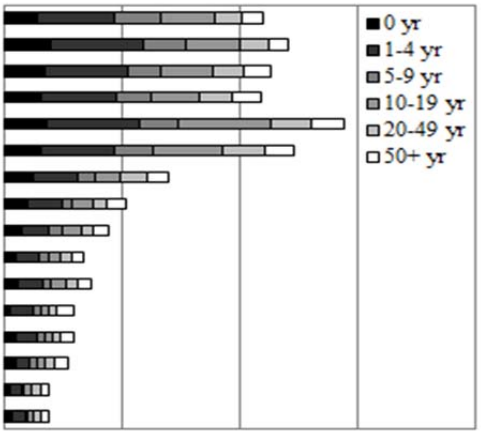
*For nine patients the age is unknown.

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

	Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
1997	72	163	96	117	56	46	550
1998	101	193	92	115	59	44	604
1999	87	174	71	109	66	57	564
2000	79	161	73	102	67	62	544
2001	91	179	82	194	86	69	719
2002	79	154	84	148	86	62	613
2003	61	97	37	53	55	45	348
2004	48	74	24	43	29	41	259
2005	37	60	28	39	25	33	222
2006	25	48	20	28	22	24	167
2007	30	51	20	30	27	28	186
2008	15	47	17	17	17	37	150
2009	24	45	17	19	15	28	148
2010	24	32	13	18	21	28	136
2011	15	23	4	16	19	19	96
2012	18	27	7	11	17	16	96

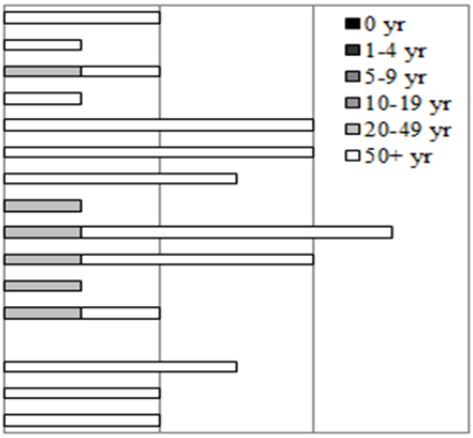
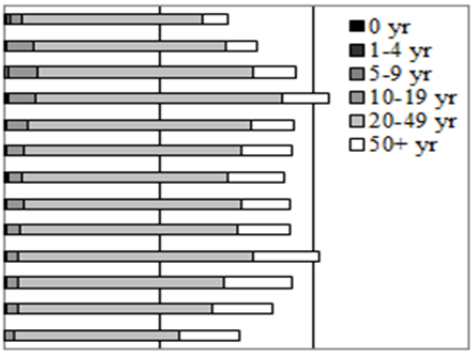
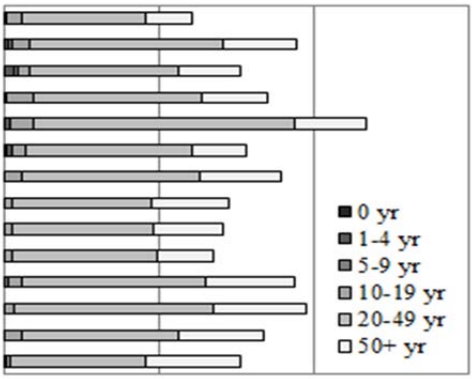
Isolates*

N



*Nontypables excluded.

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

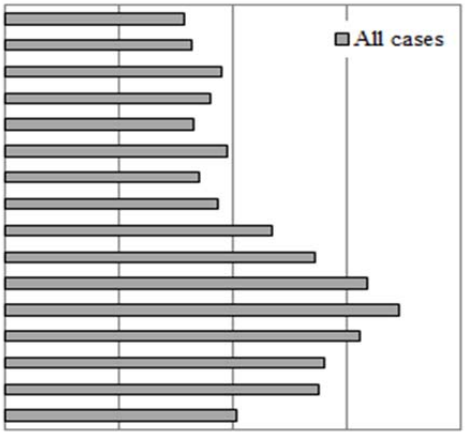
		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total	N
Mortality (B16; Acute)	1997	0	0	0	0	0	2	2	
	1998	0	0	0	0	0	1	1	
	1999	0	0	0	0	1	1	2	
	2000	0	0	0	0	0	1	1	
	2001	0	0	0	0	0	4	4	
	2002	0	0	0	0	0	4	4	
	2003	0	0	0	0	0	3	3	
	2004	0	0	0	0	1	0	1	
	2005	0	0	0	0	1	4	5	
	2006	0	0	0	0	1	3	4	
	2007	0	0	0	0	1	0	1	
	2008	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	
	2012	0	0	0	0	0	2	2	
Notifications	2000	0	18	19	76	1,167	165	1,445	
	2001	1	8	9	174	1,236	203	1,631	
	2002	1	9	17	195	1,390	269	1,881	
	2003	2	10	19	178	1,588	296	2,093	
	2004	0	9	10	130	1,440	280	1,869	
	2005	0	5	8	114	1,407	326	1,860	
	2006	2	15	9	92	1,322	365	1,805	
	2007	0	8	12	104	1,403	322	1,849	
	2008	0	9	7	89	1,398	336	1,839	
	2009	0	7	5	81	1,519	424	2,036	
	2010	0	8	11	68	1,330	441	1,858	
	2011	0	8	12	71	1,251	390	1,732	
	2012	0	4	4	58	1,066	381	1,513	
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	10	101	55	168	
	2012	0	1	1	2	88	60	153	

*For 27 patients the age is unknown.

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

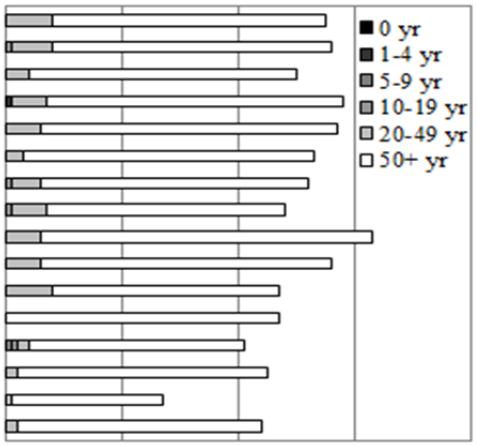
		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Laboratory diagnoses	1997	-	-	-	-	-	-	787
	1998	-	-	-	-	-	-	819
	1999	-	-	-	-	-	-	950
	2000	-	-	-	-	-	-	904
	2001	-	-	-	-	-	-	827
	2002	-	-	-	-	-	-	974
	2003	-	-	-	-	-	-	849
	2004	-	-	-	-	-	-	932
	2005	-	-	-	-	-	-	1,174
	2006	-	-	-	-	-	-	1,361
	2007	-	-	-	-	-	-	1,588
	2008	-	-	-	-	-	-	1,725
	2009	-	-	-	-	-	-	1,553
	2010	-	-	-	-	-	-	1,401
	2011	-	-	-	-	-	-	1,377
	2012	-	-	-	-	-	-	1,020

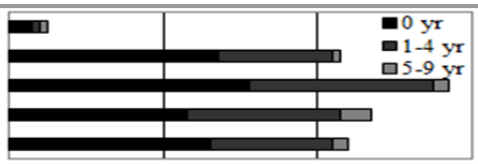
N

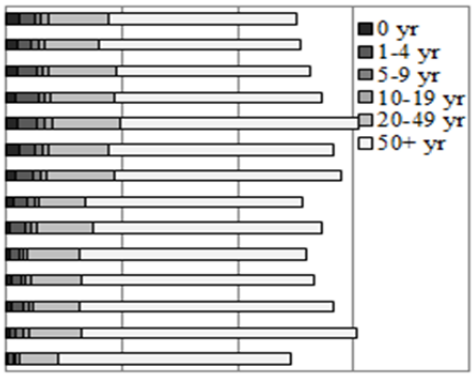


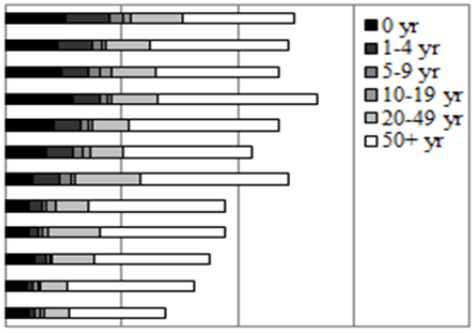
Pneumococcal disease **ICD9 0382, 481, 4823, 3201** **ICD10 J13, 18.0, 18.9, G00.1, A40.4**

		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	
	2012	0	0	0	0	2	42	44	
Notifications	2008	3	1	1*	-	-	-	5	
	2009	27	15	1*	-	-	-	43	
	2010	31	24	2*	-	-	-	57	
	2011	23	20	4*	-	-	-	47	
	2012	26	16	2*	-	-	-	44	
Hospitalisations**	1999	124	126	63	52	529	1,622	2,521	
	2000	113	110	60	53	476	1,727	2,544	
	2001	108	170	53	48	576	1,676	2,638	
	2002	97	188	61	42	544	1,796	2,734	
	2003	109	171	56	71	587	2,047	3,057	
	2004	120	144	66	44	523	1,930	2,832	
	2005	94	146	68	51	580	1,951	2,899	
	2006	76	116	56	45	400	1,860	2,557	
	2007	42	124	53	48	488	1,963	2,727	
	2008	34	92	35	31	451	1,941	2,590	
	2009	54	79	38	47	435	2,012	2,672	
	2010	64	85	50	43	390	2,200	2,839	
	2011	37	57	64	52	452	2,370	3,034	
	2012	24	44	18	29	343	2,001	2,462	
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	
	2012	20	6	4	3	22	83	138	





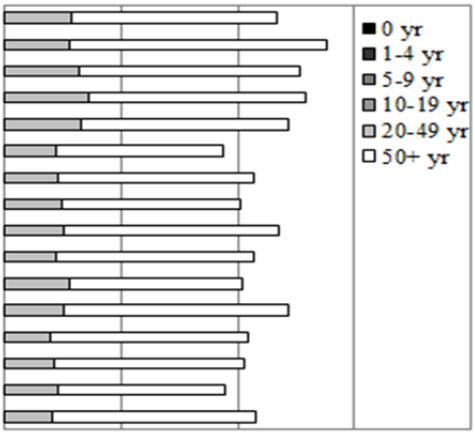




*Notifiable for 0- to 5-year-old children.
**For 91 patients the age is unknown.

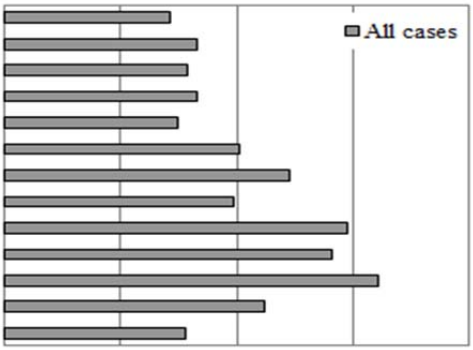
HPV **ICD9 -** **ICD10 C53**

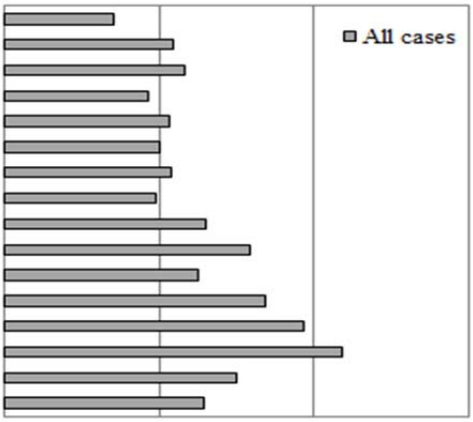
		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total	N
Mortality (Cervical cancer)	1997	0	0	0	0	58	176	234	
	1998	0	0	0	1	56	219	276	
	1999	0	0	0	0	64	189	253	
	2000	0	0	0	0	73	185	258	
	2001	0	0	0	0	66	177	243	
	2002	0	0	0	0	45	142	187	
	2003	0	0	0	0	47	167	214	
	2004	0	0	0	0	49	154	203	
	2005	0	0	0	0	52	183	235	
	2006	0	0	0	0	44	170	214	
	2007	0	0	0	0	57	147	204	
	2008	0	0	0	0	51	193	244	
	2009	0	0	0	0	40	169	209	
	2010	0	0	0	0	43	162	205	
	2011	0	0	0	0	46	143	189	
	2012	0	0	0	0	42	173	215	



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

		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total
Hospitalisations (estimation)	2000	-	-	-	-	-	-	2,864
	2001	-	-	-	-	-	-	3,312
	2002	-	-	-	-	-	-	3,160
	2003	-	-	-	-	-	-	3,322
	2004	-	-	-	-	-	-	3,000
	2005	-	-	-	-	-	-	4,063
	2006	-	-	-	-	-	-	4,903
	2007	-	-	-	-	-	-	3,948
	2008	-	-	-	-	-	-	5,895
	2009	-	-	-	-	-	-	5,641
	2010	-	-	-	-	-	-	6,442
	2011	-	-	-	-	-	-	4,487
	2012	-	-	-	-	-	-	3,112
Laboratory diagnoses	1997	-	-	-	-	-	-	712
	1998	-	-	-	-	-	-	1,094
	1999	-	-	-	-	-	-	1,163
	2000	-	-	-	-	-	-	932
	2001	-	-	-	-	-	-	1,067
	2002	-	-	-	-	-	-	1,004
	2003	-	-	-	-	-	-	1,079
	2004	-	-	-	-	-	-	975
	2005	-	-	-	-	-	-	1,304
	2006	-	-	-	-	-	-	1,585
	2007	-	-	-	-	-	-	1,251
	2008	-	-	-	-	-	-	1,691
	2009	-	-	-	-	-	-	1,935
	2010	-	-	-	-	-	-	2,180
	2011	-	-	-	-	-	-	1,504
	2012	-	-	-	-	-	-	1,287





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
	2012	0	0	0	0	0	2	2
Hospitalisations	2000	44	95	14	6	38	14	211
	2001	62	104	19	3	36	9	233
	2002	47	113	17	4	29	9	219
	2003	78	121	10	6	41	17	273
	2004	89	115	20	7	26	12	269
	2005	64	119	9	1	28	17	238
	2006	108	132	17	4	33	19	313
	2007	69	92	19	4	24	23	231
	2008	74	111	19	3	38	26	271
	2009	67	92	18	6	37	22	242
	2010	81	136	21	7	39	31	315
	2011	67	118	13	5	34	40	277
	2012	63	96	17	6	29	42	253

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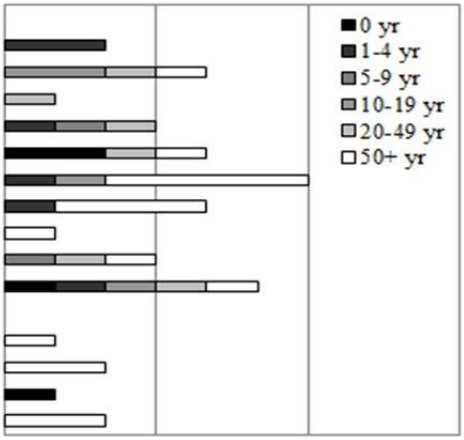
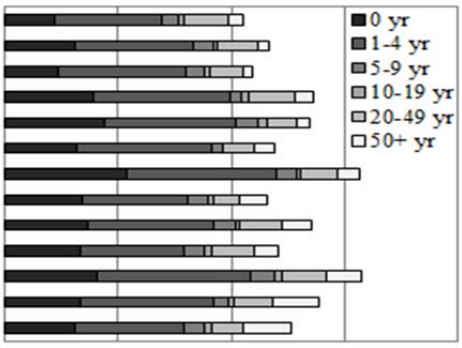
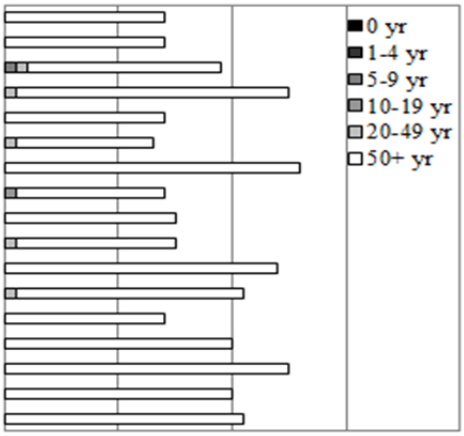
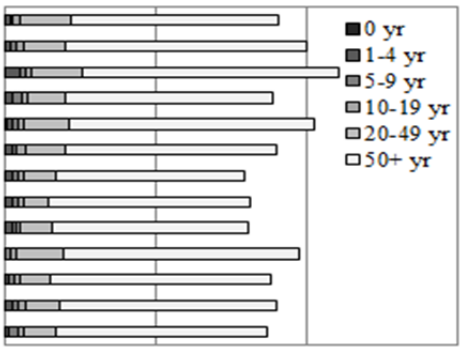


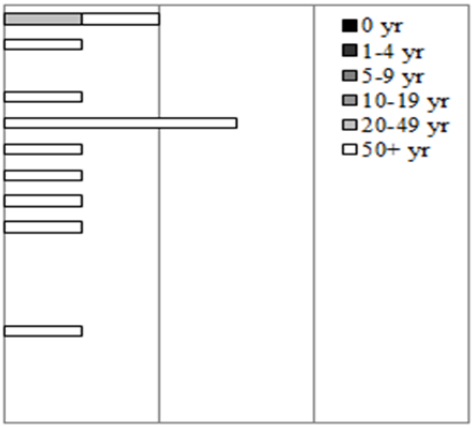


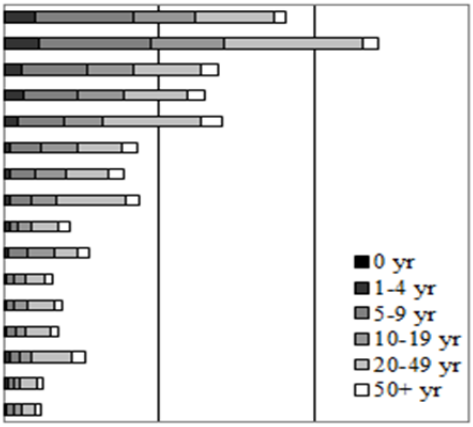
Herpes zoster (Shingles) **ICD9 053** **ICD10 B02**

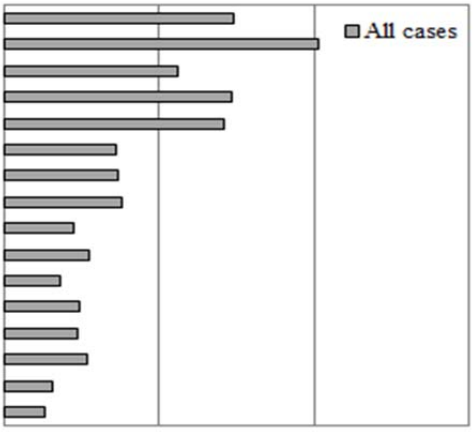
		Age (Years) 0	1-4	5-9	10-19	20-49	50+	Total	N
Mortality	1997	0	0	0	0	0	14	14	
	1998	0	0	1	0	1	17	19	
	1999	0	0	0	0	1	24	25	
	2000	0	0	0	0	0	14	14	
	2001	0	0	0	0	1	12	13	
	2002	0	0	0	0	0	26	26	
	2003	0	0	0	1	0	13	14	
	2004	0	0	0	0	0	15	15	
	2005	0	0	0	0	1	14	15	
	2006	0	0	0	0	0	24	24	
	2007	0	0	0	0	1	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	
	2012	0	0	0	0	0	21	21	
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	44	288	360	
	2012	1	6	11	8	42	279	347	

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
	2012	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
	2012	0	10	21	26	42	22	121
Laboratory diagnoses	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
	2012	-	-	-	-	-	-	53







Appendix 2 Overview of changes in the NIP since 2000

Table A1 NIP 1 July 2001 – 31 August 2002
(Change: aP added at four years of age, for all children born on or after 1 January 1998).

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

*Four doses: at 2, 3, 4 and 11 months, respectively.

Table A2 NIP 1 September 2002 – 28 February 2003
(Change: MenC added at 14 months of age, for all children born on or after 1 June 2001)*

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
0-1 year**	DTwP-IPV	DTwP-IPV vaccine/NVI	Hib	Hib vaccine/NVI
14 months	MMR	MMR vaccine/NVI	**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.
**Four doses: at 2, 3, 4 and 11 months respectively.

Table A3 NIP 1 March 2003 – 31 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 1 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

*The table indicates the birth cohort from which children received at least one injection of the newly introduced vaccination.
**Four doses: at 2, 3, 4 and 11 months respectively.
***Only children at least one of whose parents was born in a country where hepatitis B is moderately or highly endemic and children whose mother had tested positive for HBsAg.

Table A4 NIP 1 January 2005 – 31 December 2005
(Change: wP replaced by aP at 2, 3, 4 and 11 months of age, for all children born on or after 1 February 2004)*

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
0-1 year**	**DTaP-IPV/Hib**	**Infanrix IPV+Hib/GSK**	HBV***	HBVAXPRO/SP MSD
14 months	MMR	MMR vaccine/NVI	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

*The table indicates the birth cohort from which children received at least one injection of the newly introduced vaccination.
**Four doses: at 2, 3, 4 and 11 months respectively.
***Only children at least one of whose parents was born in a country where hepatitis B is moderately or highly endemic and children whose mother had tested positive for HBsAg.

Table A5 NIP 1 January 2006 – 31 May 2006
(Change: HBV added at birth for children whose mother had tested positive for HBsAg; and Infanrix IPV+Hib/GSK replaced by Pediacel/SP MSD at 2, 3, 4 and 11 months, for all children born on or after 1 February 2005)*

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
At birth	**HBV****	**HBVAXPRO/SP MSD**		
0-1 year***	**DTaP-IPV-Hib**	**Pediacel/SP MSD**	HBV****	HBVAXPRO/SP MSD
14 months	MMR	MMR vaccine/NVI	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

*The table indicates the birth cohort from which children received at least one injection of the newly introduced vaccination.
** Only for children whose mother tested positive for HBsAg.
***Four doses: at 2, 3, 4 and 11 months respectively.
****Only children at least one of whose parents was born in a country where hepatitis B is moderately or highly endemic and children whose mother had tested positive for HBsAg.

Table A6 NIP from 1 June – July/August 2006
(Change: pneumococcal vaccination added at 2, 3, 4 and 11 months of age, for all children born on or after 1 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 1 April 2006 [as a consequence an HBV vaccination at three 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

*Four 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 whose mothers had tested positive for HBsAg.
**Four doses at 2, 3, 4 and 11 months respectively.
***Only children at least one of whose parents was born in a country where hepatitis B is moderately or highly endemic and children whose mother had tested positive for HBsAg.

Table A7 NIP from July/August 2006 – 31 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 four years of age born from July/August 2002 onwards. This DTaP-IPV vaccine replaced the DT-IPV given previously at four years of age; in September/October 2006 the MMR vaccine NVI was 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

*Four 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 whose mothers had tested positive for HBsAg.
**Four doses: at 2, 3, 4 and 11 months respectively.
**Only children at least one of whose parents was born in a country where hepatitis B is moderately or highly endemic and children whose mother had tested positive for HBsAg.

Table A8 NIP from 1 January 2008 - September 2008
(Change: in 2008 the hepatitis B vaccination for children with Down syndrome born on or after 1 January 2008 was included in the NIP; from July to mid-December 2008 Pediacel/SP MSD was replaced by Infanrix IPV+Hib/GSK at 2, 3, 4 and 11 months; from February 2008 Infanrix IPV/GSK was also available for four-year-olds; from September 2008 MMR vaccine/NVI was 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 was 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**

*Four 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 whose mothers had tested positive for HBsAg.
**Four doses at 2, 3, 4 and 11 months, respectively.
***Only children at least one of whose parents was born in a country where hepatitis B is moderately or highly endemic and children whose mother had tested positive for HBsAg.
****Used until March 2008.

Table A9 NIP from September 2008 - 1 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**

*Four doses: at 2, 3, 4 and 11 months respectively.
**In 2009, only MMRVaxPro was 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 whose mothers had tested positive for HBsAg.
**Four doses: at 2, 3, 4 and 11 months respectively.
***Only children at least one of whose parents was born in a country where hepatitis B is moderately or highly endemic and children whose mother had tested positive for HBsAg.
****In 2009 only MMRVaxPro was administered

Table A10 NIP from 1 January 2010 – 1 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 no longer used)

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**		

*Four doses: at 2, 3, 4 and 11 months respectively.
**Only girls were vaccinated and received three doses of HPV vaccine: at 0,1 and 6 months.

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 whose mothers tested positive for HBsAg.
**Four doses: at 2, 3, 4 and 11 months respectively.
***Only children at least one of whose parents was born in a country where hepatitis B is moderately or highly endemic and children whose mother had tested positive for HBsAg.
****Only girls were vaccinated and received three doses of HPV vaccine: at 0,1 and 6 months.

Table A11 NIP from 1 March 2011 – 1 August 2011
(Change: the pneumococcal vaccine Prevenar/Wyeth was replaced by Synflorix/GSK for children born on or after 1 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		

*Four doses: at 2, 3, 4 and 11 months respectively.
**Only girls were vaccinated and received three doses of HPV vaccine: at 0,1 and 6 months.

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 whose mothers had tested positive for HBsAg.
**Four doses: at 2, 3, 4 and 11 months respectively.
***Only children at least one of whose parents was born in a country where hepatitis B is moderately or highly endemic and children whose mother had tested positive for HBsAg.
****Only girls were vaccinated and received three doses of HPV vaccine: at 0,1 and 6 months.

Table A12 NIP from 1 August 2011 onwards
(Change: hepatitis B vaccination for all children born on or after 1 August 2011 was 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		

*Four doses: at 2, 3, 4 and 11 months respectively.
**Only girls were vaccinated and received three doses of HPV vaccine: at 0,1 and 6 months.

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 whose mothers had tested positive for HBsAg.
**Four doses: at 2, 3, 4 and 11 months respectively.
***Only girls were vaccinated and received three doses of HPV vaccine: at 0,1 and 6 months.

Appendix 3 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	Purified pertussis toxoid (PT) 20 µg
acellular pertussis vaccine, inactivated	Purified filamentous haemagglutinin (FHA) 20 µg
poliomyelitis vaccine	Purified fimbrial agglutinogens 2 and 3 (FIM) 5 µg
and conjugated *Haemophilus influenzae*	Purified pertactin (PRN) 3 µg
type b-vaccin (adsorbed)	Inactivated type 1 poliovirus (Mahoney) 40 DU
0.5 ml	Inactivated type 2 poliovirus (MEF-1) 8 DU
	Inactivated type 3 poliovirus (Saukett) 32 DU
	Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate) 10 µg
	conjugated to tetanus toxoid (PRP-T) 20 µg
	absorbed to aluminium phosphate 1.5 mg
DT-IPV vaccine/NVI	Diphtheria-toxoid* > 5 IU
RVG 17641	Tetanus toxoid* > 20 IU
Diphtheria (adsorbed), tetanus	Inactivated poliovirus type 1 > 40 DU
(adsorbed) and inactivated poliomyelitis	Inactivated poliovirus type 2 > 4 DU
vaccine	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	Pneumococcal polysaccharide serotype 9V* 2 µg
vaccine (adsorbed)	Pneumococcal polysaccharide serotype 14* 2 µg
0.5 ml	Pneumococcal oligosaccharide serotype 18C* 2 µg
	Pneumococcal polysaccharide serotype 19F* 2 µg
	Pneumococcal polysaccharide serotype 23F* 2 µg
	*conjugated to the CRM197 carrier protein and 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	Pneumococcal polysaccharide serotype $5^{1,2}$ 1 µg
vaccine (adsorbed)	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	conjugated to tetanus toxoid 10-20 µg
vaccine (adsorbed)	adsorbed to aluminium hydroxide 0.5 mg Al^{3+}
0.5 ml	

Infanrix Hexa/GSK	
EU/1/00/152	Adsorbed diphtheria toxoid > 30 IU
Diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), inactivated poliomyelitis vaccine and conjugated *Haemophilus influenzae* type b-vaccine (adsorbed)	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
0.5 ml	Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU Adsorbed purified capsular polysaccharide of Hib (PRP) 10 µg covalently bound to tetanus toxoid (T) 20-40 µg
MMR Vax /SP MSD	Mumps virus (Jeryl Lynn) > 5000 TCID50 (tissue culture infectious doses)
RVG 17672	
Mumps, measles and rubella vaccine	Measles virus (Schwartz) > 1000 TCID50
0.5 ml	Rubella virus (Wistar RA 27/3) > 1000 TCID50
Infanrix IPV + Hib / GSK	Adsorbed diphtheria toxoid > 30 IU
RVG 22123 / RVG 34567	Adsorbed tetanus toxoid 20 - 40 IU
Diphtheria, tetanus, pertussis (acellular component), inactivated poliomyelitis vaccine and conjugated *Haemophilus influenzae* type b-vaccine (adsorbed)	Adsorbed pertussis toxoid (PT) 25 µg Adsorbed filamentous haemagglutinin (FHA) 25 µg Absorbed pertactin (PRN) 8 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU
0.5 ml	Inactivated type 3 poliovirus (Saukett) 32 DU *Haemophilus influenzae* type b polysaccharide 10 µg
Infanrix IPV / GSK	Adsorbed diphtheria toxoid > 30 IU
RVG 34568	Adsorbed tetanus toxoid > 40 IU
Diphtheria, tetanus, pertussis (acellular component), inactivated poliomyelitis vaccine	Adsorbed pertussis toxoid (PT) 25 µg Adsorbed filamentous haemagglutinin (FHA) 25 µg Absorbed pertactin (PRN) 8 µg
0.5 ml	Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU
M-M-R VaxPro / SP MSD	Mumps virus (Jeryl Lynn) > 12,500 TCID50 (tissue culture infectious doses)
EU/1/06/337/001	
Mumps, measles and rubella vaccine	Measles virus (Enders' Edmonston) > 1000 TCID50
0.5 ml	Rubella virus (Wistar RA 27/3) > 1000 TCID50
Engerix-B Junior	Hepatitis B-virus surface antigen, recombinant* (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.*

T.M. Schurink-van 't Klooster et al.

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