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

The National Immunisation Programme in the Netherlands

Surveillance and developments in 2013-2014

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Publiekssamenvatting

Het Rijksvaccinatieprogramma in Nederland
Surveillance en ontwikkelingen in 2013-2014

Weinig mensen krijgen de ziekten waartegen zij via het Rijksvaccinatieprogramma (RVP) worden gevaccineerd. De vaccinatiegraad is in Nederland al jaren hoog en het vaccinatieprogramma is veilig. Er worden relatief weinig bijwerkingen gerapporteerd en deze zijn doorgaans niet ernstig van aard. Dit blijkt uit het jaaroverzicht 2013-2014 van het RIVM. Continue monitoring is nodig om een optimaal vaccinatieprogramma te behouden.

Wijzigingen in het vaccinatieschema in 2013-2014
Het aantal prikken tegen pneumokokken in het vaccinatieschema is vanaf november 2013 met één prik verlaagd naar drie. Dit gebeurde op advies van de Gezondheidsraad omdat dit verminderde aantal evenveel bescherming biedt. Sinds januari 2014 is de vaccinatie voor meisjes tegen het HPV-virus, dat baarmoederhalskanker kan veroorzaken, teruggebracht naar twee prikken. De vaccinatie wordt aan alle twaalfjarige meisjes aangeboden. Als meisjes na hun vijftiende verjaardag met de vaccinatie starten, zijn nog wel drie prikken nodig.

Ontwikkelingen bij ziekten
Tussen mei 2013 en februari 2014 vond een grote uitbraak van mazelen plaats, vooral in gebieden waar weinig mensen zich laten vaccineren. In totaal zijn 2640 personen met mazelen gemeld, van wie er 182 zijn opgenomen in het ziekenhuis. Een persoon is overleden.
In juni 2013 was er een uitbraak van rodehond op een orthodox-gereformeerde school met een lage vaccinatiegraad. Er zijn 54 personen met rodehond gemeld. Dit was het grootste aantal sinds 2004-2005.

In 2013 zijn in Nederland geen meldingen gedaan van difterie, polio en tetanus. Na de grote epidemie in 2012 nam kinkhoest sterk af. Ook het aantal bofgevallen daalde ten opzichte van 2010-2012, een periode waarin bof veelvuldig onder studenten voorkwam. Het aantal meldingen van acute hepatitis B was in 2013 het laagst sinds 1976. Het aantal meningokokken C-ziekten is enorm gedaald sinds de introductie van de vaccinatie in 2002. Sinds de uitbreiding van het vaccin tegen pneumokokken met drie typen in 2011 is het aantal ziekten dat door die drie typen wordt veroorzaakt, gedaald.

Andere ontwikkelingen
In 2013 zijn wereldwijd in acht landen gevallen van polio aangetroffen, waaronder in Syrië. Daarom worden Syrische vluchtelingen jonger dan vijf bij aankomst in een Nederlands asielzoekerscentrum gevaccineerd tegen polio. Verder zijn de routinematige controles in gebieden met een lage vaccinatiegraad geïntensiveerd en uitgebreid naar regio's in Nederland waar vluchtelingen opgevangen worden.

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

Abstract

The National Immunisation Programme in the Netherlands
Surveillance and developments in 2013-2014

Low incidences of diseases included in the National Immunisation Programme (NIP) have been reported. Participation in the NIP has been high for many years and relatively few side effects were reported, which are usually mild and transient. This information is included in the annual report of the National Institute of Public Health and the Environment (RIVM). Continuous monitoring of effectiveness and safety is necessary for the programme to remain optimal.

Changes in the vaccination schedule in 2013-2014
Since November 2013, the number of doses given against pneumococcal disease has been reduced to three. The Dutch Health Council advised reducing the number of doses against pneumococcal disease in the vaccination schedule because research showed that one dose less gives similar protection.
Since January 2014, girls have been receiving a reduced number of doses against human papillomavirus (HPV). Two doses of HPV vaccine is offered to 12-year-old girls. If girls start with the vaccination after their 15th birthday, three doses are still necessary.

Trends in incidences of disease
From May 2013 until February 2014, a large outbreak of measles occurred in the Netherlands. Mainly areas with low vaccination coverage were affected. Overall, 2,640 measles cases were reported, 182 of which were hospitalised. One person died.
In June 2013, an outbreak of rubella occurred at an Orthodox reformed school with low vaccination coverage. In total, 54 cases of rubella were reported, which was the largest number since 2004-2005.

In 2013, no cases of diphtheria, polio and tetanus were reported. After the large epidemic in 2012, the incidence of pertussis was low in 2013. In addition, the incidence of mumps declined in 2013 compared with 2010-2012, when an outbreak occurred among students. The number of notifications of acute hepatitis B in 2013 was the lowest since 1976. Since the introduction of the vaccination in 2002, the incidence of meningococcal C disease has decreased enormously. Introduction of the 10-valent pneumococcal vaccine in 2011 reduced the number of invasive pneumococcal diseases caused by the additional PCV10 serotypes in the vaccinated age groups.

Other developments
In 2013, polio cases were found in eight countries worldwide, including Syria. Syrian refugees under 5 years of age receive vaccination against polio on arriving at the asylum seekers' centre in the Netherlands. Furthermore, the environmental routine surveillance programme has been intensified in areas with low vaccination coverage and was extended to the region in the Netherlands where refugees are first cared for.

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

Preface

This report presents an overview of the surveillance and developments in 2013-2014 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: 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, an overview of vaccines for infectious diseases tested in clinical trials that are relevant for the Netherlands is included in this report.

The report is structured as follows: Chapter 1 gives a short introduction. Recent results on vaccination coverage are discussed in Chapter 2 and public acceptance of vaccination and communication of the NIP in Chapter 3. Adverse events following immunisation (AEFI) are described 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 and the pathogen. The results of current and ongoing studies and international developments are described. Chapter 6 describes potential new target diseases, which are under consideration for inclusion in the future NIP. Finally, in Chapter 7 an overview is given of vaccines for infectious diseases which are being tested in clinical trials and are relevant for the Netherlands. In Appendix 1, the surveillance methods used to monitor the NIP are described and in Appendix 2 mortality and morbidity figures from 1997 onwards are reported from various data sources. Appendix 3 gives an overview of changes in the NIP since 2000 and in Appendix 4 the composition of vaccines used in 2013-2014 is presented.

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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 (MenC) disease, hepatitis B, pneumococcal disease and human papillomavirus (HPV)). Furthermore, surveillance data is presented with regard to potential target diseases for which a vaccine is available (rotavirus, varicella zoster virus (VZV), hepatitis A, meningococcal serogroup B (MenB) 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 at the ages of 2, 3, 4 and 11 months, simultaneously with vaccination against pneumococcal disease at 2, 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.

Changes in the vaccination schedule
Since November 2013, children have been receiving only three doses of the pneumococcal vaccine, i.e., the dose at 3 months of age has been cancelled. Starting in 2014, 12-year-old girls will be vaccinated against HPV with a two-dose schedule (0, 6 months).

Dutch Caribbean
The immunisation programme on Saba and St Eustatius is similar to the Dutch programme after implementation of the vaccines against pneumococcal disease, MenC and HPV in the recent years. In 2013, Bonaire implemented the MenC vaccination into their programme (cohort 2013) and has substituted the whole cell pertussis vaccine and hepatitis B vaccine for the hexavalent paediatric combination vaccine.

Vaccination coverage
Vaccination coverage in the Netherlands is high. However, the second MMR vaccination does not reach the required 95% participation. Participation in the NIP decreases somewhat as children get older.

Acceptance of vaccination and communication
Overall, most parents and child vaccine providers have a positive attitude towards childhood vaccinations in the NIP. A system has been developed to monitor the acceptance of vaccination among parents and child vaccine providers. An interactive web-based education tool will be developed to increase HPV vaccination uptake among girls. Both professionals and the public should be better informed about new vaccines (e.g. varicella, rotavirus) not included in the NIP so that no potential health gains are left untapped.

Adverse events
In 2013, Lareb received 1,223 reports of a total of 2,437 adverse events following immunisation (AEFI), of which the spectrum is mostly in line with past years. No signals emerged indicating that vaccines used in the NIP would be unsafe.

Diphtheria
In 2013 and 2014, up until week 24, no cases of diphtheria were reported in the Netherlands.

Pertussis
The incidence of pertussis notifications in 2013 (20 per 100,000 population) was low, compared with the estimate made during the large epidemic in 2012 (83 per 100,000). The prevalence of pertactin-deficient (i.e. a component of acellular vaccines) strains was 8% in 2013, compared with 18% in the first 5 months of 2014. Since the introduction of acellular pertussis in the primary series, vaccine effectiveness of the infant vaccinations has remained high until the preschool booster dose. The estimated vaccine effectiveness of the preschool booster dose remains high for about 4 years. Thereafter, vaccinated children become more easily infected with *Bordetella pertussis*.
Maternal immunisation has been recommended and implemented in several countries other than the Netherlands to protect young, not yet fully vaccinated infants. In England, the vaccine effectiveness of maternal vaccination was estimated to be 91%, whilst no important side effects were observed.

Tetanus
In 2013 no cases of tetanus were reported and in 2014, up to week 24, one case of tetanus was reported. A bedside test for tetanus immunity might be helpful in the decision on tetanus post-exposure prophylaxis in people who state they are not adequately vaccinated.

Poliomyelitis
In 2013 and 2014, up to week 24, no cases of poliomyelitis were reported in the Netherlands. Cases of poliomyelitis have been confirmed in Syria. There has been an increase in the number of Syrian refugees in the Netherlands. All Syrian refugees below 5 years of age are vaccinated with inactivated polio vaccine (IPV) within 48 hours after arrival in the asylum seekers' centre. The environmental routine surveillance programme in the area with a high percentage of inhabitants that refuse vaccination for religious reasons has been intensified and extended to the region where refugees are first cared for.
In 2013, worldwide 407 polio cases were found in eight countries, compared with 223 cases in five countries in 2012.

***Haemophilus influenzae* serotype b (Hib) disease**
The total number of invasive diseases caused by Hib in 2013 (n=29) was comparable to the previous year (n=28). However, the incidence among 0-4 year-olds increased from 0.76 per 100,000 in 2012 (n=7) to 1.43 per 100,000 in 2013 (n=13). The number of vaccine failures in invasive Hib disease has remained stable in recent last years. Since 2004, there has been a steady increase in the number of cases caused by nontypeable Hi strains (NTHi).

Mumps
The incidence of mumps notifications declined in 2013, compared with 2010-2012. The outbreak among students stopped, while relatively more cases occurred in non-students. The incidence of the disease in the first half of 2014 was low.

Measles
Between May 2013 and February 2014, a large outbreak of measles occurred mainly among unvaccinated primary school aged children in low vaccination coverage areas ('Bible Belt'); in total, 2,640 cases were reported with 182

hospitalisations and one death. The main outbreak control intervention was to recommend early MMR vaccination for infants aged 6-14 months in 29 municipalities with a vaccination coverage <90%. RIVM provided weekly online updates of the outbreak and advice for the protection of health care workers against measles.
Before the large outbreak, a significant increase in the notification rate of measles occurred early in 2013. One of the reported measles clusters included health care workers and children not yet vaccinated against measles.

Rubella
During the first weeks of the measles epidemic in June 2013, a large but restricted rubella outbreak was identified at an orthodox reformed school with low vaccine coverage for religious reasons in the region 'Hollands Midden', where 54 related cases were reported. This was the largest rubella outbreak in the Netherlands since 2004-2005.
In 2013 a large rubella outbreak occurred in Poland. Three solitary cases with links to Poland were reported in the Netherlands in 2013, one of which could be partially genotyped (genotype 2B).

Meningococcal serogroup C disease
In 2013, six cases of MenC disease were reported. All cases were unvaccinated. The incidence of MenC disease has decreased enormously since the introduction of vaccination in 2002 to 0.04 per 100,000 population in 2013.

Hepatitis B
In 2013, the incidence of acute hepatitis B virus infections (HBV) notifications was 0.8 per 100,000 population. It has not been this low since notification started. A relatively high incidence was reported in the North-East of the country. Male homosexual contact remained the most frequently reported risk factor. Molecular surveillance suggests ongoing transmission of a genotype A strain. Recent literature suggests that screening of migrants for HBV is likely to be cost-effective.

Pneumococcal disease
The introduction of 7-valent pneumococcal conjugate vaccination (PCV7) in 2006 led to a major decrease in vaccine-type invasive pneumococcal disease (IPD). The introduction of PCV10 in 2011 reduced the number of IPD cases caused by the additional PCV10 serotypes (1, 5 and 7F) in the vaccinated age groups. Longer follow-up is needed to assess the impact of PCV10 introduction in unvaccinated age groups. The incidence of non-vaccine-type invasive pneumococcal disease (IPD) increased after introduction of PCV7, but this increase was less pronounced in 2012-2014 in all age groups.

Human papillomavirus (HPV)
Incidences of HPV-associated cancers and deaths related to HPV-associated cancers have slightly increased in the last decade in the Netherlands. Prevalence rates of HPV amongst visitors to a sexually transmitted infections (STI) clinic are high. There is a higher prevalence among women than among men. Vaccine effectiveness of the bivalent vaccine against incident and persistent infections in a prospective cohort study at approximately three years post-vaccination was estimated at 73% and 100% for HPV16/18. At the moment, there are no indications for type replacement.

Rotavirus
Incidence of rotavirus-associated gastroenteritis seen in the Netherlands in 2013 was comparable to 2012. In 2013, G1[P8] was most commonly found in the Netherlands, followed by G3P[8], G2P[4] and G4P[8].

Varicella zoster virus (VZV) infection
It is difficult to determine if changes occurred in the VZV epidemiology in 2013. The methodology for calculating the incidence of varicella and herpes zoster in general practice has changed from 2012 onwards and these data, as well as the mortality data, are not yet available for the year 2013.
The willingness to vaccinate against varicella was found to be relatively low in the Netherlands among both professionals (21%) and parents (28%).

Hepatitis A
In 2013, the number of hepatitis A infections (110 cases) remained low, as in recent years. Fifty-five percent of the Dutch cases were reported to be travel-related, mostly Morocco and Egypt.

Meningococcal serogroup B disease
In 2013, a small increase in MenB disease was seen (88 cases in 2013, compared with 76 in 2012), which is due to a small increase among 5-64 year-olds, while among the very young the incidence decreased slightly.
In March 2014, the UK Joint Committee on Vaccination and Immunisation (JCVI) recommended that the MenB vaccine should be introduced into the UK's routine immunisation schedule for children, provided it can be obtained at a cost-effective price.

Meningococcal non-B and non-C disease
In 2013, 22 (19%) meningococcal cases were caused by non-serogroup B or C types from the total of 116 cases of meningococcal disease. Most non-B and C meningococcal cases were caused by serogroups W and Y, with 7 and 14 cases respectively in 2013.

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

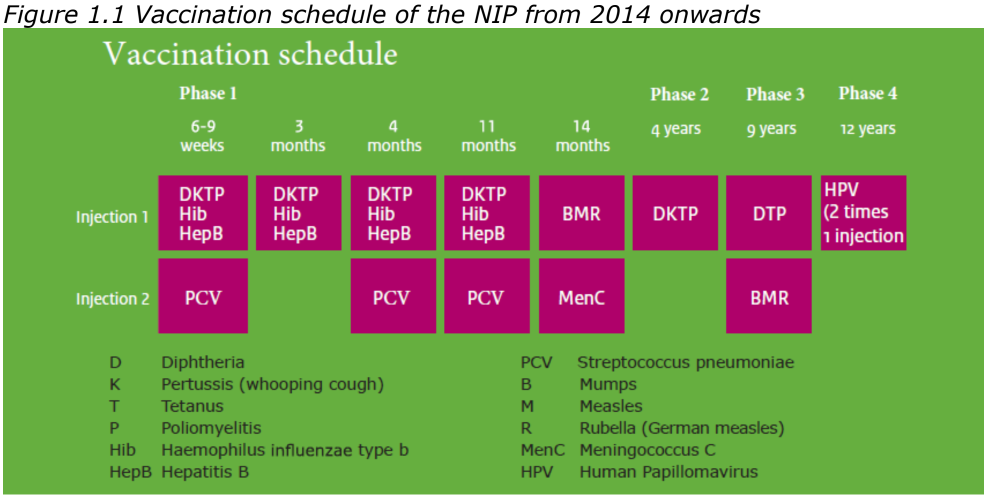
1 Introduction

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

1.1 Vaccination schedule

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, vaccinations 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) are included in the programme (Figure 1.1). Vaccinations within the NIP in the Netherlands are administered to the target population free of charge and on a voluntary basis.

Figure 1.1 Vaccination schedule of the NIP from 2014 onwards



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 those with an increased risk of morbidity and mortality following influenza. 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.

1.2 Changes in vaccination schedules

The Dutch Health Council advised on 27 November 2013 in favour of a schedule with a reduced number of doses of the pneumococcal vaccine. From then on, children receive only three doses of the pneumococcal vaccine at 2, 4 and 11 months of age.

Since January 2014, adolescent girls are vaccinated against HPV with a two-dose schedule (0, 6 months), after licensing of the bivalent vaccine for a two-dose schedule. If started after the 15th birthday, three doses are still needed.

1.3 Dutch Caribbean

The Dutch Caribbean municipalities, Bonaire, St Eustatius and Saba (BES), have expanded and adjusted their immunisation programmes in the past few years to harmonise with the Dutch NIP. Now, the immunisation programme on Saba and St Eustatius is similar to the Dutch programme after implementation of the vaccines against pneumococcal disease, MenC and HPV in recent years. In 2013, Bonaire implemented the MenC vaccination into their programme (cohort 2013) and has substituted the whole cell pertussis vaccine and hepatitis B vaccine for the hexavalent paediatric combination vaccine.
In 2013, the vaccine supply to the Dutch Caribbean municipalities, supplied up to now mostly through Pan American Health Organization (PAHO), was evaluated by the Department for Vaccine Supply and Prevention Programmes (DVP/RIVM). Based on the analysis, the Minister of Health decided to provide the vaccines from Dutch stock in future. Preparations for the distribution and delivery by mid-2015 have been started by RIVM.

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2 Vaccination coverage

E.A. van Lier

2.1 Key points

- Vaccination coverage in the Netherlands is high.
- Participation in the NIP decreases as children get older.
- Second MMR vaccination does not reach required 95% participation.

2.2 Vaccination coverage

As in previous years, the participation for the different vaccinations included in the NIP is, at 92 to 99%, high in report year 2014 (Table 2.1) [1]. The one exception is the HPV vaccination against cervical cancer, for which the participation, compared with the previous report year, increased further to 59%. Since August 2011, the NIP has expanded with a vaccination against hepatitis B; until then only children at high risk were vaccinated against hepatitis B. Among the group of infants without a high risk, 95% received this vaccination. The participation among infants from the Dutch Caribbean for the DTaP-IPV, MMR and pneumococcal vaccination is also high (90-100%).

The point of attention remains that participation in the NIP decreases as children get older. The second MMR vaccination for 9-year-olds (92%) does still not reach the required 95% participation. A participation of at least 95% is important because of the aim of the World Health Organization (WHO) Regional Office for Europe to eliminate measles from their region. Furthermore, it is very important that all children of mothers who are carriers of the hepatitis B virus receive the first extra vaccination against hepatitis B on time. Children who are infected with this virus at a young age have a higher risk of becoming a carrier. In the long term, this virus can cause serious liver disorders.

To protect infants effectively against diseases of the NIP, it is important to give vaccinations on time. The proportion of infants that received the first DTaP-IPV vaccination on time increased further from 85% to 88%. In general, infants who receive at least one vaccination through an anthroposophic child welfare centre are vaccinated less often and less timely [1].

2.3 Tables and figures

Table 2.1 Vaccination coverage per vaccine for age cohorts of newborns, toddlers, schoolchildren, and adolescent girls in 2006-2014

	Newborns*								
Report Year	**cohort**	**DTaP -IPV**	**Hib**	**Pneu ****	**MenC**	**MMR**	**HBV[a]**	**HBV[b]**	**HBV[c]**
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	
2014	2011	95.4	95.9	95.0	95.8	96.0	93.4	98.1	94.8

	Toddlers*				Schoolchildren*			Adolescent girls*	
Report Year	**cohort**	**DTaP -IPV[d]**	**DTaP -IPV[e]**	**DTaP -IPV[f]**	**cohort**	**DT -IPV**	**MMR *****	**cohort**	**HPV**
2006	2000	92.5	1.4	93.9	1995	93.0	92.9		
2007	2001	92.1	1.6	93.7	1996	92.5	92.5		
2008	2002	91.5	1.6	93.1	1997	92.6	92.5		
2009	2003	91.9	2.0	93.9	1998	93.5	93.0		
2010	2004	91.7	2.6	94.3	1999	93.4	93.1		
2011	2005	92.0	2.6	94.7	2000	92.2	92.1		
2012	2006	92.3	2.1	94.4	2001	93.0	92.6	1997	56.0
2013	2007	92.3	2.4	94.7	2002	93.1	92.9	1998	58.1
2014	2008	92.0	2.4	94.4	2003	92.7	92.4	1999	58.9

*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.

[c] Children born on or after 1 August 2011 (start universal vaccination) who do not belong to [a] or [b].

[d] Revaccinated toddlers.

[e] Toddlers that reached basic immunity at age 2-5 years and were therefore not eligible for revaccination at toddler age.

[f] Sufficiently protected toddlers (sum of [d] and [e]).

2.4 Literature

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3 Acceptance of vaccination and communication

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3.1 Key points

- Overall, most parents and child vaccine providers have a positive attitude towards childhood vaccinations in the NIP.
- A system has been developed to monitor the acceptance of vaccination among parents and child vaccine providers.
- An interactive web-based education tool will be developed to increase HPV vaccination uptake among girls.
- Both professionals and the public should be better informed about new vaccines (e.g. varicella, rotavirus) not included in the NIP so that no potential health gains are left untapped.

3.2 Acceptance of vaccination

The average vaccination coverage in the Netherlands is high (95%). It is essential that this level is sustained. The National Institute for Public Health and the Environment (RIVM), therefore, performs research to gain insight into factors that are associated with the intention to vaccinate and aims to monitor the trust in vaccination among the public and professionals. This information will be used to strengthen communication about the NIP and to perform research in this area in order to keep the vaccination coverage high. A brief description of new results from various studies is given below.

3.2.1 Monitoring system for acceptance of vaccination

For 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, a study on parental information-seeking behaviour with regard to childhood vaccination has been conducted [1]. In 2013-2014, results became available from the questionnaires that were sent to parents with at least one child under four years old in order to determine the most important factors associated with their intention to have their child vaccinated or not. Overall, parents reported a positive attitude towards childhood vaccination, which played an important role in parental intention to vaccinate. The study also showed that beliefs about vaccines were more important to the parental intention to vaccinate than were beliefs about diseases. Moral norms about vaccination influenced the attitude and intention of parents positively. Trust in the NIP is also an important determinant in parents' vaccination decisions. Most parents (81%) perceived vaccinating their child as being a self-evident choice and 83% did not think long about whether to vaccinate their child or not.
Another study was conducted to gain insight into the vaccination content people shared on the Internet during the measles outbreaks in the Netherlands. Three large peaks in the number of tweets, social media messages and online news articles were observed, which could be explained by announcements issued by the RIVM about the measles outbreak, statements of Dutch politicians and a measles-related death. The content of the messages focused on informing the public about the number of measles cases and the sentiment mostly found was frustration towards orthodox Protestants, who do not vaccinate their child for

religious reasons. Our study showed that tweets were primarily used to spread information, but were also used to share opinions and could, therefore, be used as a measure of public interest and concerns.
CVPs received a questionnaire to gain insight into CVPs' attitude towards and experience with the NIP. This study showed that CVPs have a positive attitude towards the NIP and are satisfied with how the current NIP is organised. CVPs seem to be able to recognise different groups of parents with different backgrounds who are critical towards vaccination, such as highly educated parents and anthroposophists. Some CVPs avoid having discussions with parents about the NIP, mostly due to insufficient time. CVPs take 1-2 or 2-5 minutes to inform parents about the NIP during one consultation. When they provide information to parents, they mostly focus on possible side effects and the NIP schedule. They further indicated that they are able to communicate with (critical) parents about the NIP, but would still like to receive education in how to communicate better with these parents.
The information from all the above-mentioned 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. The monitoring system will consist of different parts: (a) focus groups for parents and CVPs (only when there are major changes or events within the NIP), (b) a monthly questionnaire distributed among parents, to gain insight into the determinants that influence their vaccination decision, (c) an annual questionnaire to gain insight into CVPs' experience and attitude towards the NIP, (d) Child Welfare Centres (CWC) as a sentinel, and (e) an Internet monitor [1].

3.2.2 *Interventions to stimulate deliberate decision-making and to increase vaccine uptake*

3.2.2.1 Interactive web-based, tailored education promoting the acceptability of HPV-vaccination among the mothers of invited girls

Currently, TNO and Maastricht University are developing a website that aims to guide mothers, personally and interactively, in their decision about the HPV-vaccination of their daughter. First, three field experiments were conducted among mothers, providing input for the development of the website. Results from the first experiment showed that it seems best to provide mothers with risk information in the form of statistical numbers (i.e. numbers on prevalence), instead of narrative risk information (i.e. a personal story) or no risk information about contracting HPV and developing cervical cancer later in life. The second experiment showed that there were no differences in HPV-vaccination intention among mothers after exposing them to different types of normative information (i.e. information about opinions versus the behaviours of others, positively versus negatively framed). The third experiment showed that not addressing the uncertainties in science about the potential long-term effectiveness and side effects of the HPV-vaccination appears to be better for the promotion of HPV-vaccination uptake. However, the researchers believe that addressing these uncertainties will make mothers less vulnerable to counter arguments and less likely to look for information about these uncertainties themselves (e.g. on the Internet), which reduces the risk of exposure to incorrect information about HPV vaccination.
This year, draft versions of the website are are being built and tested. In 2015, a study will be conducted among a sampling of mothers to examine whether the website is an effective tool for mothers to help them make an informed decision about the HPV-vaccination of their daughter and whether exposure to this communication will have a higher vaccination uptake compared with the education usually provided.

3.2.2.2 Brochure on religious arguments for and against vaccination in order to stimulate deliberate decision-making among orthodox Protestants

Based on the results of the thesis entitled 'Acceptance of vaccination among orthodox Protestants in the Netherlands' [2], the Academic Collaborative Centre AMPHI Nijmegen and the NPV (a Christian patients' organisation) developed the brochure 'Vaccination: providence, trust and responsibility'. In this brochure religious arguments for and against vaccination are discussed in interviews with orthodox Protestant religious leaders. The decision-making process is discussed with orthodox Protestant parents. The aim of this brochure is to stimulate deliberate decision-making with regard to vaccination. The brochure was distributed via child health care centres in the Bible Belt and via the NPV, where it is also available online. During the measles epidemic, an extra edition was distributed to orthodox Protestant family magazines. An Internet survey among orthodox Protestants aged 18-40 years showed that more than 40% of the respondents had received the brochure — mainly via orthodox Protestant channels — while 80% of them had actually read it. They were positive on the content and layout; some stated that they were helped in forming and expressing their opinion or in discussing the subject and understanding different opinions. Reading the brochure did not result in a major change of opinion on vaccination.

3.2.3 Child vaccine providers' experiences with parents who are critical towards vaccination

Currently, a study is being conducted into the experiences of CVPs with parents who are critical towards vaccination. Parents pose their questions to CVPs, as they are seen as the most reliable source of information. When facing critical parents, CVPs might have to answer difficult questions or have discussions with them about vaccines. The goal of this study is to find out whether CVPs feel confident in answering questions from critical parents, which questions are frequently asked, whether CVPs feel there is a lack of information for critical parents and whether CVPs have suggestions to improve the provision of information. To accomplish the goal of this study, interviews will be conducted with CVPs at CWCs throughout the Netherlands. With the results of this study, the existing information for parents can be adjusted to meet the questions of (critical) parents. Furthermore, education and information can be developed in line with the needs of CVPs, to improve the consultations with critical parents.

3.2.4 Vaccines not included in a public vaccination programme and new delivery methods

3.2.4.1 Discrete choice experiment rotavirus vaccine

Vaccine effectiveness, the frequency of severe side effects, the duration of protection provided, and the out-of-pocket costs influenced parental willingness to vaccinate their newborn against rotavirus. Parents were willing to trade 17.2 percentage points in vaccine effectiveness for the lowest frequency of severe side effects (i.e. 1 in 1,000,000) or 23.2 percentage points for a higher duration of protection. Potential vaccination coverage ranged between 24.0% and 81.1%, depending on the vaccine scenario (i.e. vaccine effectiveness and the duration of protection provided) and implementation strategy (i.e. out-of-pocket costs and the health care facility that administers the vaccines).
When deciding about vaccination against rotavirus, parents are mostly driven by the out-of-pocket costs, vaccine effectiveness, the duration of protection and the frequency of severe side effects. The highest vaccination coverage is expected for a vaccine with high effectiveness and protection duration that is implemented

within the current NIP context. The implementation of the same rotavirus vaccine in the free market will result in the lowest coverage.

Vaccine development has been improved and accelerated owing to new biotechnological methods, especially DNA techniques. New vaccines are regularly becoming available. Efficacious vaccines are now available for the prevention of diseases such as chickenpox, gastroenteritis caused by rotavirus infection and shingles. However, these are rarely used in the Netherlands. As a result, potential health gains are being left untapped. One of the reasons for the under-utilisation of vaccines might be a lack of knowledge about vaccination among physicians, coupled with their lack of experience in this area. Other factors may be a limited awareness among the general public and the fact that these vaccines are not included in the basic health insurance package or are financially inaccessible for other reasons. In the Netherlands, vaccines are mainly used in the context of public vaccination programmes [3]. In response to the Health Council's advice, the Minister of Health has decided to make these new vaccines better accessible to the public outside a public programme such as the NIP. RIVM has been asked to develop professional guidelines and information for the public and professionals on a broad range of marketed vaccines. Such vaccines will be made financially accessible through the health insurance.

A questionnaire study was set up to explore the attitudes of parents to the administration of multiple vaccinations at a single visit using alternative delivery systems. Most participants had a positive attitude with respect to the jet injector and the patch as alternative vaccine delivery methods, whereas the micro needle device and an intranasal spray device were not perceived as better than the conventional syringe by the parents. Parents indicated that both the jet injector and the patch might increase their acceptance of giving their children more than two vaccinations at the same time [4].

3.3 Communication of NIP

3.3.1 Communication with public

3.3.1.1 NIP website

The NIP website, which is part of the RIVM website, no longer fully met the needs of informing the public. Much of the content was directed towards the professionals and was less applicable for the public. That is why a decision was taken to update the website for the public, specifically directed at parents. By means of an online questionnaire, two designs of the future homepage were presented to the participants belonging to the target group. The results of this questionnaire will be used to make choices about the definitive NIP website. Additionally, the results described in the thesis written by Harmsen [1] are also taken into account.

3.3.2 Communication with professionals

All information about the NIP can be found on the website. Yearly, an update of the NIP guidelines and implementation takes place and the website is updated regularly. Furthermore, the professionals in the field are informed via a regularly published newsletter. The medical advisors of the RIVM are responsible for informing the staff members of the Child Vaccine Providers. When urgent matters arise, the communication will be done by direct email or telephone.

3.4 Literature

1. Harmsen I. Vaccinating: self-evident or not?: Thesis Maastricht University, The Netherlands; 2014.
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4 Adverse events

J.M. Kemmeren, P. Huijbers, H.E. de Melker

4.1 Key points

- In 2013, Lareb received 1,223 reports with a total of 2,437 adverse events following immunisation (AEFI), the spectrum of which is mostly in line with past years.
- No signals emerged indicating that vaccines used in the NIP would be unsafe.

4.2 Passive surveillance system

The enhanced passive surveillance system, managed since January 2011 by Lareb, receives reports of AEFI for all vaccines included in the NIP.
In 2013, Lareb received 1,223 reports out of a total of 2,437 AEFI (Table 4.1) [1]. The spectrum of reported AEFI is mostly in line with past years. The majority of the reports represent well-known AEFI such as fever, crying and injection site reactions. The most (n=301) reported event and still remarkable association is the already known adverse event of 'extensive limb swelling' (ELS), which occurs in 4-year-old children after the administration of the fifth DTP-Polio vaccine (Infanrix-IPV®). In 2013, this ELS was also reported in 11 children that received the DT-IPV vaccine at 9 years of age. Apart from that, the increase in the number of reports after vaccination at the age of 9 (42 in 2012 vs 78 reports in 2013) is remarkable. The RIVM has set up a reactogenicity study to further investigate this signal.
Lareb received a small number of reports of apnoeic attacks following the vaccination of premature babies. It was already known that such attacks could occur, mostly in younger prematures. Now it was being shown that this could also occur in older prematures, born after 32 weeks of pregnancy.
The numbers of reports of fever and of crying had increased. In infants, the number of reports of hypotonic hyporesponsive episodes and discoloured legs had decreased. The coming years will show whether this is a lasting effect.
In 13-year-old girls, Lareb received fewer reports of chronic fatigue in 2013 after a sudden rise in reports of this condition in 2012 (Table 4.2).

4.3 (Inter)national developments

4.3.1 Vaccines targeting diseases included in the current NIP

4.3.1.1 DTaP-IPV-Hib-HepB

In two safety studies of DTaP-IPV vaccine recipients, there is no evidence of increased risk of adverse events [2, 3]. For women who received the Tdap vaccine during pregnancy or for their infants, no increased risk of adverse events was found compared with pregnant women who received a saline placebo injection [4]. Furthermore, the liquid pentavalent DTwP-HepB-Hib vaccine (Quinvaxem) proved to have an acceptable safety profile [5, 6] and provided evidence for the interchangeability with other pentavalent vaccines in a primary vaccination course [7]. The safety of an absorbed DTaP-vaccine with an acellulair pertussis component was evaluated in tests of acute and chronic toxicity in immature animals. The safety of these experimental samples satisfied World Health Organization (WHO) requirements [8]. A cohort study with data from the Vaccine Adverse Event Reporting System database (phase I) and a case-control study with data from the Vaccine Safety Datalink database (phase II) showed a significantly increased risk ratio for the incidence of autism

spectrum disorder reported following thimerosal-containing DTaP vaccine in comparison with thimerosal-free DTaP vaccine [9]. Although the US Center for Disease Control and Prevention insists that there is no relationship between thimerosal-containing vaccines and autism rates in children [10], this potential signal will be followed. For the NIP, this has no impact since thimerosal is not used as a preservative in routinely recommended childhood vaccines in the Netherlands.
The results from a preclinical evaluation of a *Haemophilus influenza* type b conjugate vaccine showed that this vaccine was well-tolerated and immunogenic in rats compared with a licensed vaccine [11]. Furthermore, in infants the safety profile for CRM197-conjugated Hib vaccine was comparable to a PRP-T Hib vaccine [12].
In the literature, no safety issues were found for hexavalent DTaP-HBV-IPV/Hib vaccine administered at 15 months of age, or used in a challenge dose in 7 to 8-year-old children [13, 14]. Furthermore, hepatitis B vaccination was welli tolerated in human immunodeficiency virus (HIV)-infected adults and in healthy adults who did not respond after routine primary vaccination [15, 16].

4.3.1.2 Meningococcal C

Phase III trials showed that MenACWY-CRM has an acceptable safety profile in two-month-old children [17] and in subjects ages 2 years and above [18]. Furthermore, Baxter et al. [19] showed that MenACWY-CRM can be used safely to boost adolescents who have received a primary vaccination with either MenACWY-CRM or MenACWY-D. MenACWY-TT was also well-tolerated in healthy subjects aged 18-25 years (phase III trial) [20]. Two reviews confirmed this result [21, 22].

4.3.1.3 Mumps, measles, rubella (MMR)

In order to provide the evidence for perfecting the immunisation strategy of MMR, He et al. [23] evaluated the safety of MMR on a schedule with the first dose at 8 months or 12 months of age. No safety issues were found. Hambidge et al. [24] found no significant association between vaccination in the first year of life and acute seizure events regardless of vaccine type and regardless of whether the vaccine was received on time or delayed. However, in the second year of life, delay of the first MMR vaccine until 16 months of age or older resulted in a higher risk of seizures than when the administration of the MMR vaccine occurred on time. This effect was also found by Rowhani-Rahbar et al. [25]. The findings of Wilson [26] suggest that girls may have an increased reactogenicity to MMR vaccines, which may be indicative of general sex differences in the responses to the measles virus. In patients with DiGeorge syndrome with mild-to-moderate immunosuppression, MMR vaccine was generally well-tolerated [27].
Diaz-Ortega [28] found that aerosolised vaccines were as safe as injected vaccines.

4.3.1.4 HPV

Along with the introduction of the HPV vaccines, several cases of onset or exacerbations of autoimmune diseases following HPV vaccination have been reported in the literature and pharmacovigilance databases, triggering concerns about its safety. The HPV vaccination programme, however, has been introduced in a population that is at high risk for the onset of autoimmune diseases, making it difficult to assess the role of HPV vaccine in these cases. No association was found between bivalent HPV vaccination and chronic fatigue syndrome [29] and

between quadrivalent HPV vaccination and Guillain-Barre syndrome [30]. A clinically acceptable safety profile was also reported for the bivalent HPV vaccine up to 4 years after first vaccination [31]. Pellegrino et al. [32] analysed and reviewed all case reports and studies dealing with either the onset of an autoimmune disease in a vaccinated subject or the safety in patients with autoimmune diseases in order to define the role of the HPV vaccine in these diseases and hence its safety. They concluded that vidence of a causal relationship was provided in few cases in the examined studies. It has been suggested that the possibility of a genetic predisposition to vaccine-induced autoimmune disease may explain these findings. Therefore they advise investigating actively the identification of genetic bases for adverse events following vaccination in order to provide a useful tool to prevent rare and serious diseases without impacting negatively on public confidence in immunization programmes. So, the ongoing vigilance for the safety of these vaccines remains important.
The results of a phase I study showed that a new Escherichia coli-expressed recombinant HPV 16/18 bivalent vaccine is well-tolerated in healthy women [33]. Van Damme et al. [34] conducted two phase I/II studies to compare the safety of investigational tetravalent HPV L1 virus-like particle (VLP) vaccines, containing VLPs from two additional oncogenic genotypes, with licensed HPV 16/18 AS04-adjuvanted vaccine in healthy 18-25 year-old women. They showed that the reactogenicity in the 7-day post-vaccination period tended to increase with the introduction of additional VLPs, especially for formulations containing AS01.

4.3.1.5 Pneumococcal disease

For PCV10, no significant increase in the risk of injection site abscess was observed between the injection sites of the PCV10 vaccine from a two-dose vial without preservative and DTaP-HBV-Hib vaccine [35]. Several trials were performed to check the safety of PCV13. PCV13 proved to have a favourable safety profile in infants and toddlers [36-38]. Administered to older children and adolescents, PCV13 was also shown to be safe [39]. However, simultaneous trivalent inactivated influenza vaccine and PCV13 administration was associated with higher transient increased fever risk than administration of either vaccine without the other product [40]. A meta-analysis showed that PCV13 has a favourable safety profile, similar to that of PCV7 [41]. In the field of adult pneumococcal vaccination, an expert panel concluded that there is sufficient safety evidence to use PCV13 in adults over 50 years of age [42]. For PCV7, Liakou et al. [43] concluded that additional PCV7 doses could be safely given to children with idiopathic nephrotic syndrome. PPV23 was shown to be safe in patients with systemic lupus erythematodes (SLE) [44], in HIV-infected patients [45] and in elderly individuals with chronic lung disease [46]. Vaccination with PHiD-CV was well-tolerated in infants, toddlers and children up to 59 months of age [47-50].
New vaccines containing highly conserved *Streptococcus pneumoniae* proteins, such as pneumolysin toxoid and histidine-triad protein D, are being developed to provide broader protection against pneumococcal disease. Investigational vaccine formulations containing dPly and PhtD were well-tolerated when administrated to toddlers as a 2-dose primary vaccination followed by a booster dose [51], as well as in healthy adults as stand-alone protein vaccine or combined with PHiD-CV conjugates [52]. In a phase I trial, Berglund et al. [53] investigated a protein-based nontypeable *Haemophilus influenzae* and pneumococcal vaccine (HiP) containing dPly, PhtD and NTHi protein D. No

serious adverse events were reported. However, HiP combined with the AS03 adjuvant appeared to be more reactogenic that the antigens alone.

4.3.2 Other possible future NIP candidates

4.3.2.1 Rotavirus

A recent update of the Australian surveillance data confirmed findings from earlier years, with a relative incidence of intussusception of 6.8 (95% CI, 2.4–19.0) for Rotarix, and 9.9 (95% CI 3.7–26.4) for Rotateq in the first 7 days post dose-1 and a smaller increased risk 1–7 days after the second dose of each vaccine [54]. Furthermore, data published from three large US surveillance studies identified a small but significantly increased risk of intussusception after Rotateq (attributable risk ranging from 1 in 73,000 to 1 in 1,000,000 vaccinated infants) and a higher increased risk after Rotarix (attributable risk ranging from 1 in 19,000 to 1 in 36,000 vaccinated infants) [55-57]. Only one European study on intussusception and rotavirus vaccination has been published to date. Based on German vaccine adverse event reports, a small but insignificant increase in intussusception was observed in the 1-7 day period post vaccination for both vaccines (Rotarix standardised morbidity ratio (SMR) 1.9 (95% CI: 0.8–4.0), Rotateq SMR: 1.6 (95% CI: 0.5–3.7)) [58]. In a subgroup of infants receiving their first dose of either vaccine after 3 months of age, the increase in SMR was more pronounced and statistically significant.
The available post-marketing evidence suggests that rotavirus vaccination is associated with a small but significantly increased risk of intussusception, particularly in the first 7 days after administration of the first vaccine dose, translating into 1-5 additional cases of intussusception per 100,000 vaccinated infants. The difference in intussusception risk between the two vaccines observed in the US is remarkable and has not been confirmed in Australian or European comparative analyses. Additional post-marketing surveillance data are required to further assess risk differences between the two vaccines.

4.3.2.2 Varicella

A few years ago, a post-licensure study had shown a more than twofold elevated risk of febrile convulsions after first dose vaccination with the combined MMRV vaccine (ProQuad), compared with separately administered MMR+V vaccines. This finding was confirmed by Schink et al. [59], who showed a risk of febrile convulsion similar in magnitude to Priorix-Tetra, suggesting a class effect for these quadrivalent vaccines. Higher frequencies of fever were also seen for MMRV vaccines, compared with MMR+V and MMR vaccines in studies conducted by Prymula et al. [60] and Cha et al. [61].
In patients with DiGeorge syndrome that had mild-to-moderate immunosuppression, the varicella vaccine was generally well-tolerated [27].

4.3.2.3 Herpes zoster

Several studies evaluated the safety of herpes zoster vaccination in adults. In a phase II trial, Chlibek et al. [62] showed that use of the adjuvant AS01 retains acceptable safety and reactogenicity profiles. The results from another phase II trial demonstrated that three formulations of gE/AS01B were well-tolerated in adults aged =60 years [63]. Furthermore, vaccination with a live attenuated zoster vaccine appeared to be safe in hematopoietic stem cell transplantation recipients (Zostavax) [64], in patients with SLE (Zostavax) [65], in immunocompromised adults (a heat-treated zoster vaccine) [66] and in elderly people with or without diabetes (Oka Strain) [67]. Serious adverse events are very rare and mostly described in immunocompromised patients. Leung et al.

[68] described the death of a 15-month-old girl who developed a varicella-like rash 20 days after varicella vaccination. Clinical symptoms were suggestive of a primary or acquired immune deficiency. In addition, Maves et al. [69] described a man with previously-undiagnosed HIV infection who received VZV vaccination and subsequently displayed disseminated varicella, respiratory failure, and sepsis.

4.3.2.4 Hepatitis A

A study which investigated the efficacy and safety of hepatitis A vaccination in kidney transplant recipients showed that the vaccine was well-tolerated in all patients [70]. Another study assessed the safety of a virosomal hepatitis A vaccine compared with an aluminium-absorbed hepatitis A vaccine in Indian children aged 18-47 months [71]. The overall incidence of adverse events (solicited and unsolicited) after each vaccination was similar in both groups. Both vaccines were well-tolerated.

4.3.2.5 Meningococcal B

There is one phase II study published which examined the impact of prophylactic paracetamol on the occurrence of fever and other solicited reactions to 4CMenB and MenC vaccines. Occurrence of fever was higher in infants co-administered with 4CMenB, compared with those given a MenC vaccine, but it was significantly decreased by prophylactic paracetamol, as were other solicited reactions to vaccination, both local and systemic. Co-administration of 4CMenB had an acceptable tolerability profile, with no withdrawals due to vaccination-related adverse events [72]. In an assessment report about 4CMenb (Bexsero®), the EMA noted a possible association between this vaccine and convulsions, with or without fever and Kawasaki disease [73]. Therefore, the potential risk, such as febrile seizures and Kawasaki disease, will be investigated in a post-licensure observational safety study as part of the phamacovigilance activities.

4.4 Tables and figures

Table 4.1 Number of reports per dose and suspected vaccine(s)

Vaccines	Total 2012	**Total 2013**	2 m	3 m	4 m	11 m	BMR-0	14 m	4 yr	9 yr	12-13 yr (three doses respectively)		
Infanrix hexa® + Synflorix®	500	**497**	208	114	70	105							
Infanrix hexa®	30	**20**	5	1	5	9							
Synflorix®	10	**11**	4	3		4							
MMRvaxPro® + NeisVac-C®	93	**110**						110					
MMRvaxPro®	45	**37**					11	23		3			
NeisVac-C®	4												
Infanrix-IPV®	423	**335**							335				
DTP-NVI	9	**11**								11			
MMRvaxPro® + DTP-NVI	42	**78**								78			
Cervarix®	104	**82**									42	14	26
Pediacel® + Prevenar®	21												
Pediacel® + Synflorix ®	40												
Infanrix hexa ® + Prevenar®	6												
Pediacel®	7												
Vaccines outside vaccination schedule or vaccination time unknown	53	**42**											
Total	1387	**1223**	217	118	75	118	11	133	335	92	42	14	26

Source: Lareb [1]

Table 4.2 Reported adverse events per vaccination moment

Vaccines	Total 2012	**Total 2013**	2m	3m	4m	11m	BMR-0	14m	4yr	9yr	12-13 yr (three doses respectively)			Other
Death	3	**4**	1	2										1
Injection site reactions	555	**558**	41	37	19	58	2	11	301	48	11	3	8	19
Abnormal body temperature	501	**560**	115	58	32	66	7	81	102	52	16	3	8	20
Infections	95	**55**	11	2	2	10	1	15	5	2	2		2	3
Malaise and fatigue	160	**133**	35	22	13	7		4	15	7	10	5	9	6
Allergic reaction	13	**12**	2	1	2			2	2	1	1			1
Disorders of the immune system	7	**3**				1		2						
Crying	157	**274**	93	52	27	27	4	32	24	8				7
Haematological disorders	2	**3**	1						1					1
Gastrointestinal complaints	165	**177**	48	19	13	10	2	15	16	20	11	5	10	8
Respiratory symptoms	21	**25**	8	3	3	3	1	3	1	1	1		1	
Cardiovascular diseases	4	**9**	4	2									3	
Muscle and joint disorders	26	**57**	7		1	2			15	8	12	2	8	2
Skin symptoms	180	**215**	24	22	14	31	6	67	14	13	14			10
Discoloured legs	40	**17**	9	5	3									
Headache/dizziness	61	**100**	1					2	12	39	17	6	20	3
Fainting	144	**93**	32	10	9	3	1	4	13	10	5	2	2	2
Apnoeic attacks	54	**59**	4	6	3	14		22	4	1	1			4
Other disorders of the nervous system	38	**41**	8	4	2	4		8	4	4	2		3	2
Other disorders	34	**42**	1		1	2		11	4	4	6	2	4	7
Total	2260	**2437**	445	245	144	238	24	279	533	218	109	28	78	96

Source: Lareb [1]

4.5 Literature

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5 Current National Immunisation Programme

5.1 Diphtheria

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5.1.1 Key points

- In 2013 and in 2014 until week 24, no cases of diphtheria were reported in the Netherlands.

5.1.2 Epidemiology

In 2013 and in 2014 up to week 24, no diphtheria notifications were received (Figure 5.1.1).

5.1.3 Pathogen

In 2013, the RIVM received three *Corynebacterium diphtheriae* strains, compared with two *Corynebacterium diphtheriae* strains in 2014 up to week 24. Three were suspected to be cutaneous diphtheria and two nose-isolates. All strains were tested as diphtheria-toxin-PCR negative strains. Since 2003, participation in the External Quality Assurance Study for Laboratory Diagnosis of Diphtheria (EU DIP-net) has been used to monitor the quality level of the laboratory diagnosis, to compensate for the lack of cases.

5.1.4 Tables and figures

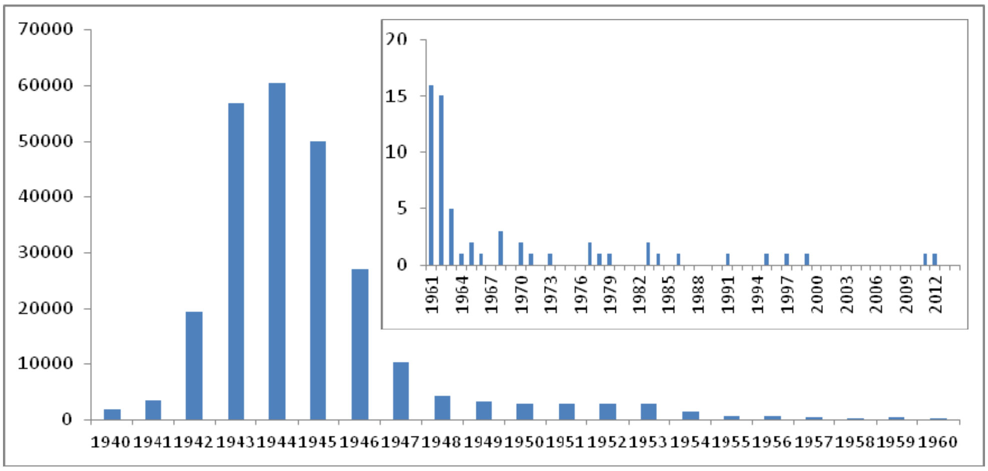

Figure 5.1.1 Notifications of diphtheria for 1940-1960 and 1961-2013

5.2 Pertussis

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5.2.1 Key points

- The incidence of pertussis notifications in 2013 (20 per 100,000) was low compared with the estimate during the large epidemic in 2012 (83 per 100,000).

- Since the introduction of acellular pertussis in the primary series, vaccine effectiveness of the infant vaccinations has remained high until the preschool booster dose.
- Estimated vaccine effectiveness of the preschool booster dose remains high for about 4 years. Thereafter, vaccinated children become more frequently infected with *Bordetella pertussis*.
- Maternal immunisation has been recommended and implemented in several countries other than the Netherlands to better protect young, not yet fully vaccinated infants.
- In England, vaccine effectiveness of maternal vaccination was estimated at 91%. No important safety signals were observed.
- The prevalence of pertactin-deficient (i.e. a component of acellular vaccines) strains was 8% in 2013 compared to 18% in the first 5 months of 2014.

5.2.2 Epidemiology

5.2.2.1 Disease

Following the large outbreak in 2012, numbers in 2013 were the lowest since 2003 (Figure 5.2.1). A slight increase in notifications was seen in the first quarter of 2014. Age-specific incidence rates were low for all categories, compared with 2000-2012 (Figure 5.2.2).
Data on hospitalisations and deaths, according to Statistics Netherlands (CBS), over 2013 were not available yet. Among the notifications, 1 death was reported in a 6-week-old unvaccinated infant.

5.2.2.2 Vaccine effectiveness

In Figure 5.2.3, vaccine effectiveness (VE) estimated through the �można screening method’ for the infant vaccination series is shown. We would like to emphasize that the presented VE should not be interpreted as being ‘true’ absolute efficacies. The data are used to study trends in VE estimations. In 2005, an infant combination vaccine with an acellular pertussis component was introduced in the NIP, resulting in an increase of VE of the primary series for 1-3 year-olds [1]. In the initial years after introduction, the VE for 2 and 3 year-olds was lower than the current estimates, because these children still received the whole-cell vaccine during infancy. From 2007 onwards, the VE for 1 to 3 year-olds remained well above 80%.
The 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 5.2.1).

5.2.2.3 Cost-effectiveness

Lugnér et al. investigated the cost-effectiveness of three vaccination strategies in the Netherlands: vaccination of the neonate or the mother directly after birth (cocooning), or the mother during pregnancy (maternal). These measures can help to decrease the pertussis burden in newborns. Cocooning was the most attractive option and resulted in an incremental cost-effectiveness ratio (ICER) of €89,000/QALY [2].
The American Advisory Committee on Immunization Practices (ACIP) advised in 2012 that all adults aged =65 years should receive a single dose of tetanus, diphtheria and acellular pertussis vaccination. McGarry et al. compared clinical and economic outcomes of this intervention compared with current practice using a dynamic model [3]. For the US population, the intervention is expected to prevent >97,000 cases (>4,000 severe and >5,000 among infants) of pertussis annually. Additional vaccination costs are $4.7 million. Net cost

savings, including vaccination costs, are $47.7 million. From a societal perspective, the intervention strategy is dominant (less costly and resulting in more than 3,000 QALYs) versus baseline.

5.2.3 *Pathogen*

Strain surveillance focuses primarily on the analysis of *Bordetella pertussis* antigens that are used in acellular pertussis vaccines: pertussis toxin (Ptx), pertactin (Prn), filamentous hemagglutinin, serotype 2 fimbriae (Fim2) and serotype 3 fimbriae (Fim3). Both changes in genotype and phenotype are monitored to identify novel antigenic variants and strains that are deficient in one or more vaccine components, respectively. With one exception, no major shifts were found compared with previous years (2010-2013). The exception concerned the emergence of strains that are deficient in Prn. The Prn-deficient strains were observed for the first time in 2010. The prevalence fluctuated between 1% and 8% in the years 2010-2013. In 2014, we observed an increase to 18%. This percentage is, however, based on only 21 strains. In countries where acellular pertussis vaccines have been used longer than in the Netherlands, prevalences of Prn-deficient strains have been found between 14% and 55%. It should be noted that, in previous years, filamentous haemagglutinin (FHA)-deficient strains have also been detected at low prevalences (<1%). In collaboration with the Radboud UMC (Dr. D. Diavatopoulos), an experiment using a mouse model was performed to study whether acellular vaccines were less effective against Prn-deficient strains than against wild type strains. Preliminary results do indeed show indications for lower VE. These results need to be confirmed in further experiments.

5.2.4 *Research*

In ongoing immunological studies in mice, we are investigating whether unfavourable T cell differentiation profiles after acellular pertussis vaccination can be reverted by adding water soluble Th1/Th17 stimulating adjuvants. Furthermore, in humans the immune modulating effect of currently circulating pertussis strains, including vaccine antigen deficient strains, on innate immune responses is being studied. Also, mechanisms of waning and aging of human pertussis-specific immune responses will continue to be studied using clinical samples from the 'SKI-study' and it's follow-up, the 'Imm-f@ct study'.
In a longitudinal study, we are investigating the B and T cell memory immune responses in 9-year-old children fully vaccinated with the acellular vaccine. The children included in the study received Boostrix as a second booster vaccine at 9 years of age and will be monitored until a year after the booster vaccination (KIM-study). In a second study, the humoral and cellular responses of adults aged 25-29 years will be analysed after a booster vaccination with Boostrix. The participants in this so-called VIKING study have only been vaccinated in their first year of life with a whole-cell vaccine.

Studies on the effect of Prn-deficiency on vaccine efficacy need to be confirmed. We also plan to compare the efficacy of two, three and five component pertussis vaccines against Prn-deficient strains. In theory, a five component vaccine should be more effective against Prn-deficient strains than two or three component vaccines. Recent results suggest that another vaccine component, FHA, is down regulated in vaccinated mice. We will also investigate whether this affects vaccine efficacy. Finally, our work on the characterisation and spread of Prn-deficient strains by whole genomic sequencing, proteomics and transcriptomics will be continued. One of the aims of this work is to identify mutations, which compensate for the lack of Prn production. Such mutations may lead to new, more effective vaccine components.

In a clinical study using clinical samples from pertussis patients (SKI-study), it was found that the size of the specific memory B cell population induced early after pertussis infection appeared to increase with age [4], while the breadth of the long-term memory T cell response was found to decrease with age [5]. This indicates that various age-related mechanisms co-occur and may influence pertussis immunity.
Memory B and T cell responses have been studied in children 6 years of age at 2 years after the booster vaccination in children who had been primed with the acellular pertussis (aP) vaccine. Even two years after booster vaccination at 4 years of age in aP-primed children, pertussis-specific antibody levels exceed pre-booster levels, memory B cells were still present and T cell responses were similar to those pre-booster [6]. Although, in general, the pertussis-specific immunological responses in these 6-year-old children seem adequate, epidemiological studies from the USA show that, as early as 4 years after the 5th acellular vaccination, children in the USA were infected during the last epidemic. This fast decrease in VE over time is also found in the Netherlands, as illustrated in Table 5.2.1 with VE-estimates ranging between 34% and 82% at 9 years of age, i.e. 5 years after the pre-school booster [7, 8]. To study this further, we are planning a longitudinal follow-up sample more than 5 years after an extra booster vaccination at 9 years in children who have been primed with a whole-cell vaccine.

5.2.5 International developments

Pertussis has resurged not only in the Netherlands, but worldwide as well. In the past few years, large epidemics have been observed in e.g. Australia, the USA and the UK. It is assumed that the switch from whole-cell vaccines to acellular vaccines has contributed to the resurgence of pertussis. The effect of introducing less effective pertussis vaccines has been aggravated by pathogen adaptation. The continuing adaptation of *Bordetella pertussis* is impressive and worrying and includes antigenic divergence with vaccine strains, inactivating genes coding for vaccine components and the upregulation of virulence factors, which suppress host defences. A positive development is the introduction of maternal immunisation in many countries. Data from the UK show a good safety profile and 91% (95% CI 82-95) vaccine effectiveness of maternal immunisation [9, 10].

5.2.6 Tables and figures

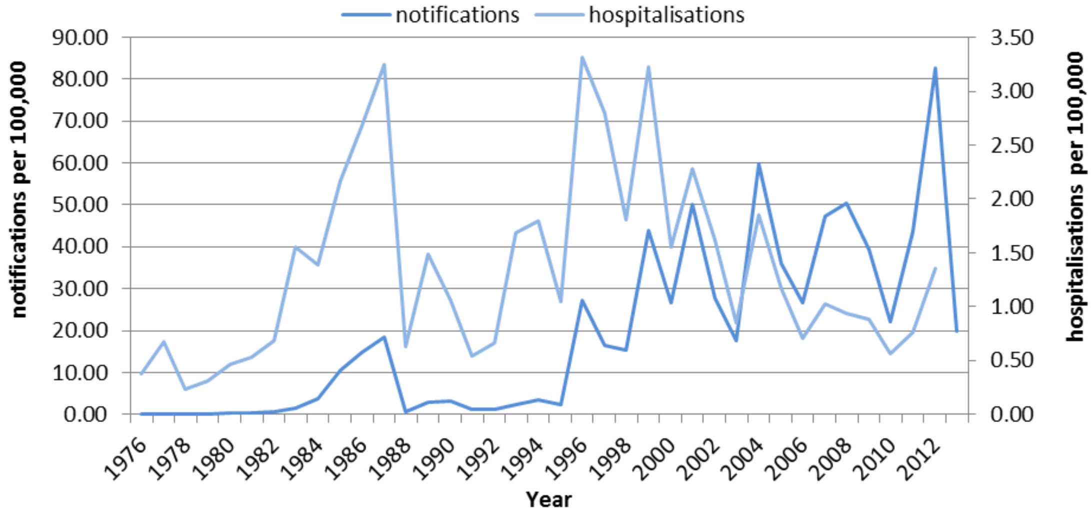

Figure 5.2.1 Notifications (left Y-axis) and hospitalisations (right Y-axis) per 100,000 for 1976-2013. Data on hospitalisations in 2013 were not known yet.

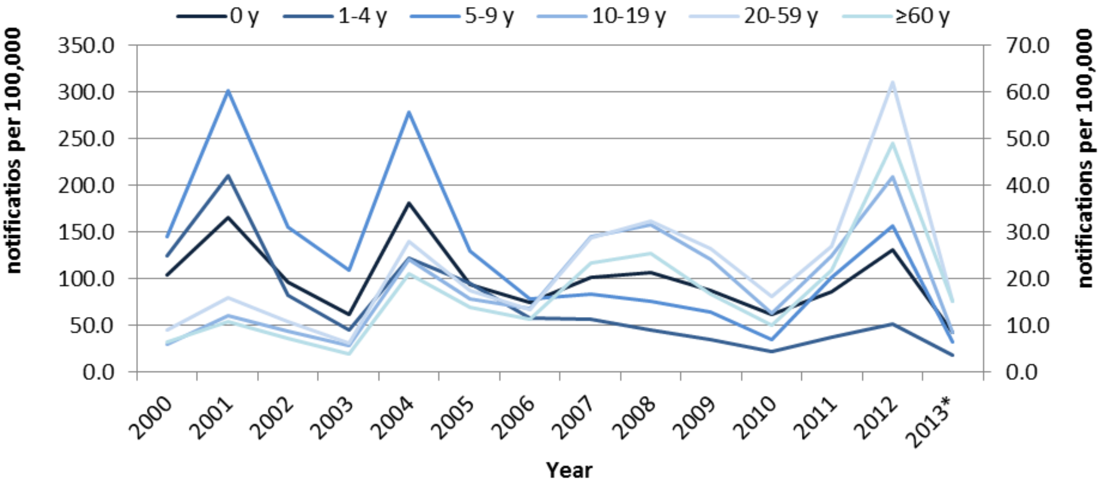

Figure 5.2.2 Notifications per 100,000 per age category for 2000-2013

*: data on 2013 contain information on notifications up to April 6th, 2014. Categories of 20-59 and =60 years are depicted on right Y-axis, the other categories on the left Y-axis.

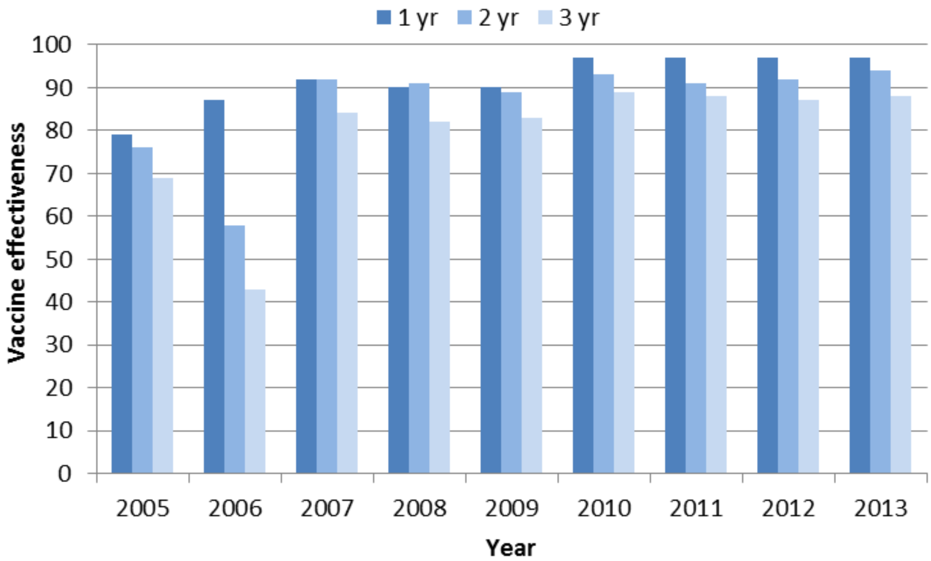

Figure 5.2.3 Vaccine effectiveness estimated for 1, 2 and 3 year-olds for 2005-2013

Table 5.2.1 Estimation of vaccine-effectiveness of the preschool booster by the 'screening method' for 5-15 year-olds per birth cohort

Birth cohort/ age	**5y**	**6y**	**7y**	**8y**	**9y**	**10y**	**11y**	**12y**	**13y**	**14y**	**15y**
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	82						
2005	83	87	86	93							
2006	93	90	82								
2007	89	86									
2008	85										

For some age groups, the proportion of vaccinated cases exceeded the vaccine coverage of the population (92%). Therefore, VE could not be estimated.

5.2.7 *Literature*

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5.3 Tetanus

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

5.3.1 Key points

- In 2013 no cases of tetanus were reported. In 2014 until week 24, one case of tetanus was reported.
- A bedside test for tetanus immunity might be helpful in the decision on tetanus post-exposure prophylaxis in people who state they are not adequately vaccinated.

5.3.2 Epidemiology

In 2013, no cases of tetanus were notified (Figure 5.3.1), whereas in 2014, until week 24, one case of tetanus was notified. This 39-year-old male was clinically diagnosed with tetanus after a dog bite. Since he was fully vaccinated (i.e. six doses of tetanus toxoid during childhood) the validity of this diagnosis is uncertain. However, his symptoms did match the clinical case definition and there was not a more plausible diagnosis.

5.3.3 Pathogen

No isolates of *Clostridium tetani* were found. *Clostridium tetani* is rarely isolated, so the diagnosis mostly depends on clinical recognition. Serological diagnosis is not possible, as infection does not lead to an antibody response.

5.3.4 Research

In the Netherlands, generally low numbers of tetanus cases are reported. Some of these cases visited a physician and did not receive proper tetanus post-exposure prophylaxis. This suggests that the Dutch Health Council (DHC) recommendations on tetanus post-exposure prophylaxis (T-PEP) are not always followed properly [1]. This was confirmed in a study on the use of T-PEP guidelines by emergency departments (EDs) and general practitioners (GPs) in the Netherlands [2]. A study on the usefulness of a bedside test for tetanus immunity among three EDs in the Netherlands is currently being analysed. Van der Maas et al. also showed the over-use of Tetanus Toxoid (TT) and under-use of Tetanus Immunoglobulins. This bedside test could be useful in people who state they are not adequately vaccinated.

5.3.5 *Tables and figures*

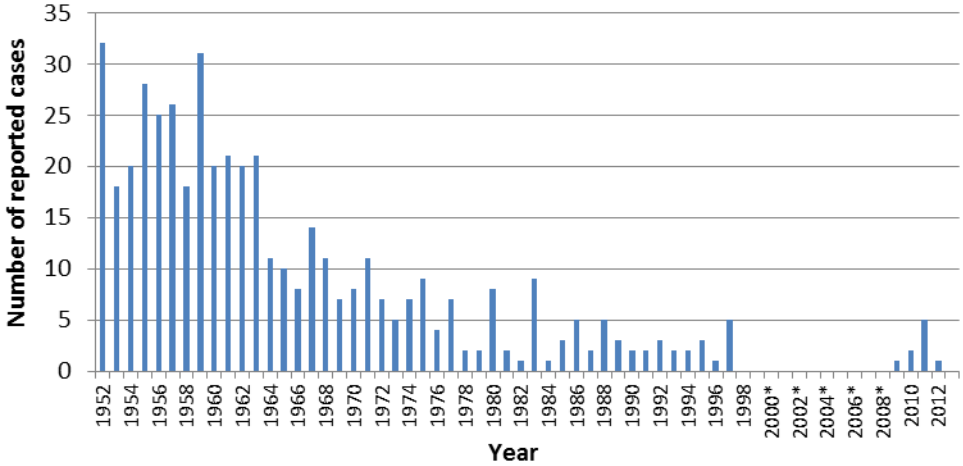

Figure 5.3.1 Reported cases of tetanus in the Netherlands by year, 1952-2013
**Between 1999 and 2009 tetanus was not notifiable.*

5.3.6 *Literature*

1. te Wierik MJ, Hahné SJ, van Ooik PC, van Lier AM, Swaan C. [Tetanus prophylaxis after an injury; check the need for vaccination and immunoglobulin]. Nederlands tijdschrift voor geneeskunde. 2013;157(38):A5906. Tetanusprofylaxe na verwonding: check de indicatie voor vaccinatie en immunoglobuline.
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5.4 Poliomyelitis

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

5.4.1 Key points

- In 2013 and 2014 up to week 24, no cases of poliomyelitis were reported in the Netherlands.
- Cases of poliomyelitis have been confirmed in Syria.
- There has been an increase in the number of Syrian refugees in the Netherlands. All Syrian refugees below 5 years of age are vaccinated with inactivated polio vaccine (IPV) within 48 hours after arrival in the asylum seekers' centre.
- The environmental routine surveillance programme, in the area with a high percentage of inhabitants that refuse vaccination for religious reasons, has been intensified and extended to the region where refugees are first cared for.
- Silent wild poliovirus circulation in water stools of healthy persons without cases of poliomyelitis has been demonstrated in Israel up to April 2014, despite large-scale vaccination programmes with oral polio vaccine (OPV).
- In 2012, worldwide 223 polio cases were found in five countries, compared with 407 cases in eight countries in 2013.

5.4.2 Epidemiology

In 2013 and 2014 up to week 24, no cases of poliomyelitis were reported in the Netherlands (Figure 5.4.1).

5.4.2.1 Global situation

In 2013, polio remained endemic in three countries: Afghanistan, Nigeria and Pakistan.
The Pakistan poliovirus spread to Israel, the West Bank and Gaza, to Syria and to Iraq. The Nigeria poliovirus spread to Somalia, Cameroon and Equatorial Guinea. In 2012, worldwide 223 polio cases were found in five countries, compared with 407 cases in eight countries in 2013 (Figure 5.4.2). The global eradication initiative is under pressure and it is unlikely that wild poliovirus will have disappeared by 2015, the target year for interrupted circulation.
Infected countries have undertaken several initiatives to reverse this negative eradication trend.

5.4.2.2 Israel

Environmental surveillance has found extended and continuous circulation of wild poliovirus type 1 in Israel without cases of paralytic polio since February 2013. The virus was also detected in sewage samples from Gaza and the West Bank. A nationwide supplementary immunisation activity (SIA) with bivalent oral polio vaccine (OPV) targeting children <10 years of age had only a limited effect: the number of positive samples, as well as the concentration of wild poliovirus in these samples, has gone down, but wild poliovirus-positive sewage samples were detected up to April 2014.

5.4.2.3 Syria

In October 2013, cases of wild type poliovirus causing poliomyelitis were reported in Syria.
Vaccination campaigns in refugee camps in neighbouring countries started immediately, even before confirmation of the cases in Syria. All Syrian asylum

seekers below five years of age who come to the Netherlands are vaccinated with inactivated polio vaccine (IPV) within 48 hours after arrival. Furthermore, the environmental surveillance programme, routinely performed in the traditional risk area with a high percentage of inhabitants that refuse vaccination for religious reasons, has been intensified and extended to the region where refugees are first cared for.

5.4.3 *Pathogen*

In 2013 and 2014 up to week 24, no polio virus was found during the routine surveillance activities in the Netherlands.
Worldwide, vaccine-derived polioviruses (VDPVs) are still found (Figure 5.4.3). VDPVs can originate in two ways: by continued circulation of OPV viruses in unprotected populations or by prolonged excretion by immune-deficient persons.

5.4.4 *International developments*

WHO has launched the Polio Eradication and Endgame Strategic Plan 2013-2018 with four objectives:

1. detection and interruption of all poliovirus circulation;
2. strengthening immunisation systems and withdrawal of OPV (to start with OPV2);
3. containment of poliovirus and certification of interruption of transmission;
4. planning the legacy of polio.

The Polio Eradication and Endgame Strategic Plan 2013-2018 addresses the eradication of all polio disease, whether caused by wild poliovirus or circulating vaccine-derived poliovirus, while planning for the backbone of the polio effort to be used for delivering other health services to the world's most vulnerable children.
After 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) prevents emergence of new type 2 circulating VDPVs (cVDPVs), the most frequently observed serotype to develop into 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 soon 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, WHO has called for new polio vaccines [1, 2]. In response, following the demonstration of a proof of principle in the 1990s [3], Intravacc (former part of RIVM and the Netherlands Vaccine Institute) continued the development of a Sabin-IPV (Inactivated Poliovirus Vaccine, based on attenuated 'Sabin' polio virus strains).
The developed technology is intended to be transferred to local vaccine manufacturers in low and middle–income countries [4]. The transfer of technology at the first individual manufacturer site (Panacea, India) was started in 2012. In collaboration with WHO, five other potential partners from South Korea, China (two times), Mexico and India were selected. Future partners will receive the existing Sabin-IPV production process and related quality control (QC) testing and are encouraged to participate in further optimisation of the actual process in order to make the vaccine more affordable.

5.4.5 Tables and figures

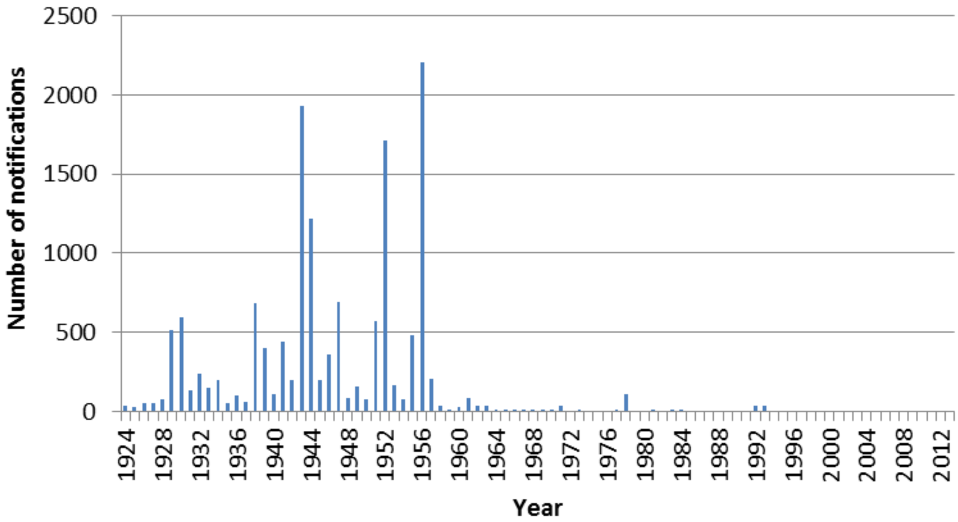

Figure 5.4.1 Notifications of poliomyelitis in 1924-2013

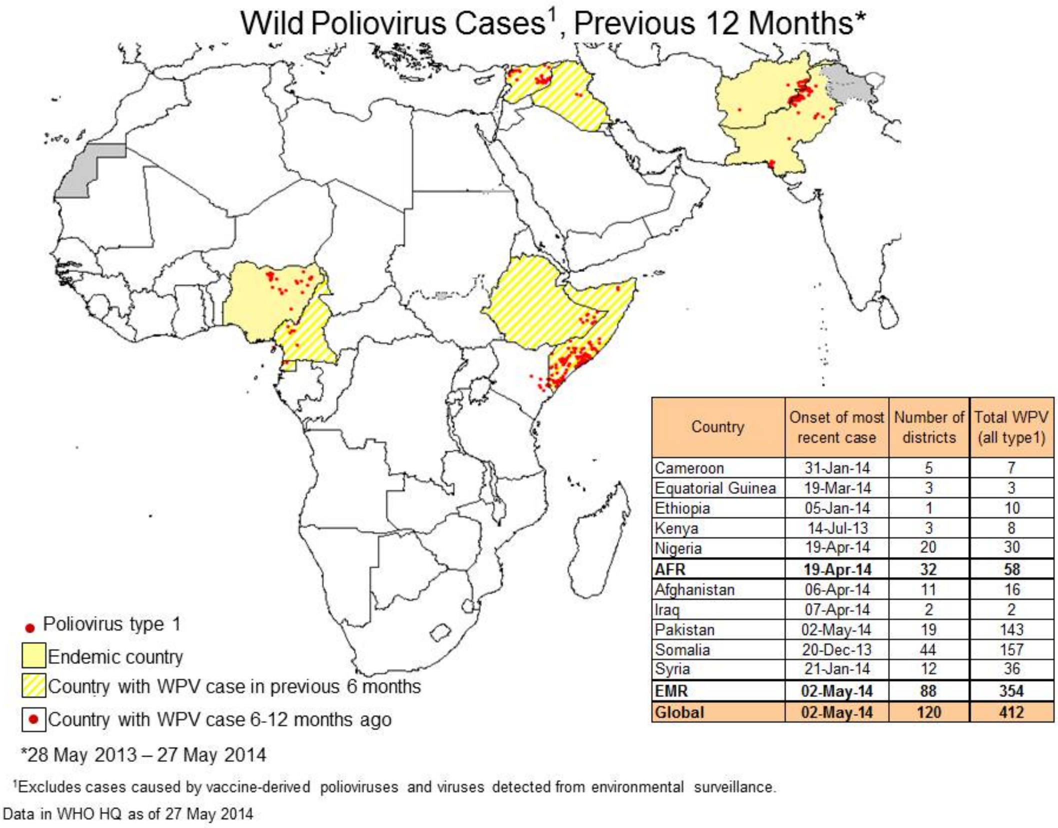

Figure 5.4.2 Wild poliovirus cases worldwide

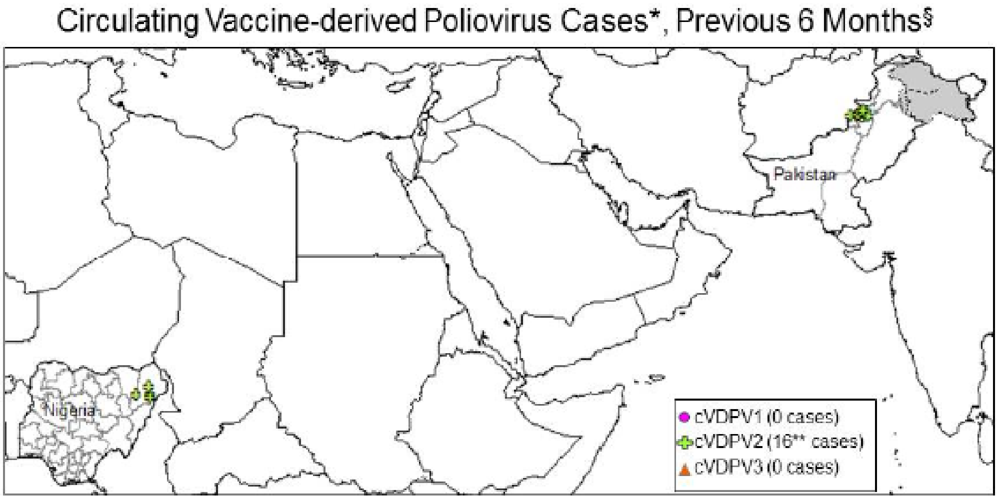

Figure 5.4.3 Circulating vaccine-derived Poliovirus in the previous 6 months (28 November 2013-27 May 2014)

5.4.6 *Literature*

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5.5 ***Haemophilus influenzae* serotype b (Hib) disease**

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

5.5.1 *Key points*

- The total number of invasive diseases caused by *Haemophilus influenzae* serotype b (Hib) in 2013 (n=29) was comparable to the previous year (n=28). The incidence among 0-4 year-olds increased from 0.76 per 100,000 in 2012 (n=7) to 1.43 per 100,000 in 2013 (n=13).
- The number of vaccine failures of invasive Hib disease remained constant in recent years.
- Since 2004, there has been a steady increase in the number of cases caused by nontypeable Hi strains (NTHi).

5.5.2 *Epidemiology*

After the introduction of vaccination in 1993, the number of cases of Hib disease decreased from 247 in 1993 to 12 in 1999. However, in 2002-2005 the number of cases of Hib disease increased again, with a peak of 48 cases in 2004. Since then, the annual number of cases has varied between 22-37 cases. In 2013, the number of cases was 29 (Figure 5.5.1). Incidence is highest among 0-4 year-olds and the elderly aged 65 years and older (Figure 5.5.2). The incidence among 0-4 year-olds increased from 0.76 per 100,000 (n=7) in 2012 to 1.43 per 100,000 (n=13) in 2013.

5.5.2.1 Nontypeable Hi strains

The number of cases caused by nontypeable (unencapsulated) Hi strains (NTHi) increased from 30 in 1993 to 90 in 2003, partially because the number of blood isolates submitted for serotyping increased. From 2004 to 2013, a gradual increase of the number of cases from 71 to 114 was observed (Figure 5.5.1). In 2013, the highest incidence of NTHi was among the elderly aged 65 years and older (2.69 per 100,000).

5.5.2.2 Vaccine failures

In the cohorts eligible for vaccination, the number of infections due to Hib showed a peak in 2005 (n=29), after which it decreased until 2011 (n=7) and thereafter increased again (n=14 in 2013). The number of vaccine failures showed a similar distribution (n=17 in 2005 and n=4 in 2011), except for 2013 (n=6), when the number decreased compared with 2012 (n=9) (Figure 5.5.3).

5.5.3 Pathogen

There are no indications that the pathogenicity of Hib has changed.

5.5.4 Research

As part of the Hib technology transfer project managed by the Institute for Translational Vaccinology (Intravacc, originating from the former Vaccinology Unit of the National Institute of Public Health and the Environment (RIVM) and the Netherlands Vaccine Institute (NVI)), a new affordable and a non-infringing production process for a Hib conjugate vaccine has been developed. The technology was transferred to a number of vaccine manufacturers in India, Indonesia, and China in order to be able to increase the Hib conjugate vaccine supply. In 2014, results of a repeated dose toxicity and local tolerance study in rats were published to compare the reactogenicity and immunogenicity of the new Hib conjugate vaccine with a licensed vaccine. This makes it possible to directly evaluate the vaccine in phase 1 clinical trials conducted by other potential technology transfer partners to facilitate the way to the market [1].

5.5.5 International developments

In the past 20 years, a steady but constant increase has occurred in invasive NTHi worldwide, with perinatal infants, young children and elderly people most at risk. Individuals with underlying comorbidities are most susceptible and infection is associated with high mortality. An emerging problem is the resistance to β-lactam antibiotics among Gram-negative bacilli, involving the mechanism of the production of β-lactamases. Additionally, the emergence and spread of β-lactamase-negative ampicillin-resistant strains in many regions of the world is a concern, potentially necessitating changes to antibiotic treatment guidelines for community-acquired infections of the upper and lower respiratory tract [2].

The recently licensed ten-valent pneumococcal conjugate vaccine (Synflorix, GSK) includes protein D from *H. influenzae* as a carrier protein.
It needs to be assessed whether this vaccine (PHiD-CV) will protect against serious infection with NTHi in high-risk groups and whether the use of the pneumococcal conjugate vaccine will influence nasopharyngeal colonisation with

NTHi [2]. Note, however, that Van den Bergh et al. [3] had shown in a randomised controlled trial that PHiD-CV had no differential effect on nasopharyngeal NTHi colonisation, acquisition or density compared with 7vCRM in healthy children up to 2 years of age in the Netherlands. On the other hand, Bosch et al. [manuscript submitted] showed that carriage of *H. influenzae*, mainly NTHi, remained significantly higher in 2012-2013 compared with the pre-vaccination data for both PHiD-CV-vaccinated children aged 11 months (61% vs 46%) and PCV7-vaccinated children aged 24 months (68% vs 52%), but was similar to results in 2009 and 2011. In the parents, carriage of *H. influenzae* had returned to the carriage rate observed before implementation of PCV7.
Clinical trials assessing efficacy of PHiD-CV against AOM (NCT00839254 and NCT00466947) are currently ongoing.

5.5.6 Tables and figures

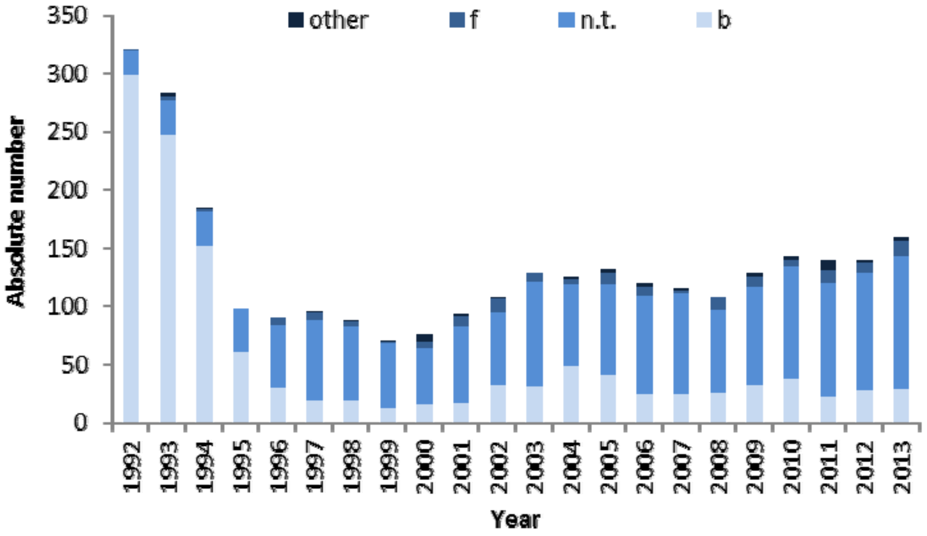

Figure 5.5.1 Absolute number of H. influenzae isolates by serotype, 1992-2013

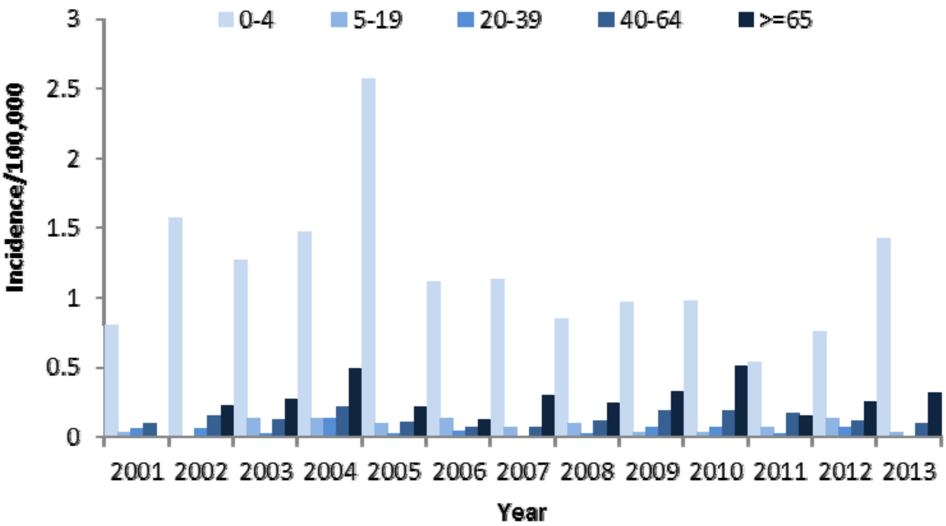

Figure 5.5.2 Age-specific incidence of invasive Hib disease, 2001-2013

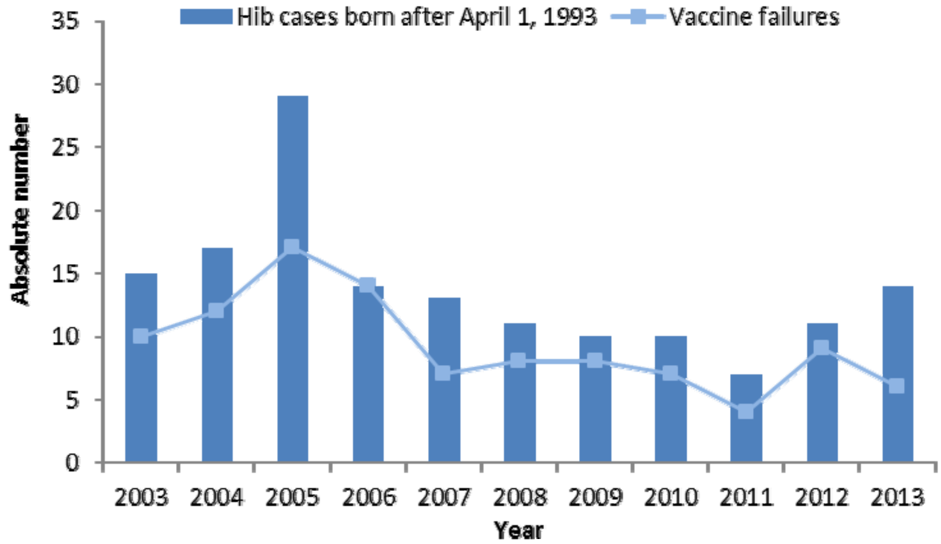

Figure 5.5.3 Annual number of Hib infections in people eligible for vaccination (i.e. born after April 1, 1993) and the number of vaccine failures, 2003-2013

5.5.7 *Literature*

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5.6 **Mumps**

L. Nic Lochlainn, S. Gouma, N. Rots, T.M. Schurink-van 't Klooster,
R. van Binnendijk, S. Hahné

5.6.1 *Key points*

- The incidence of mumps notifications declined in 2013 compared with the years before. The outbreak among students stopped while relatively more cases occurred in non-students. The incidence in the first half of 2014 was low.

5.6.2 *Epidemiology*

Following the introduction of mumps vaccination in the NIP in 1987, there was a large decline in the incidence of mumps in the Netherlands. First signs of an increase were observed in 2004 with an outbreak among students [1]. Subsequently, an outbreak occurred among unvaccinated schoolchildren in the Bible Belt (2007-2009) [2]. Since late 2009, an increase in mumps has occurred among students. Three epidemic seasons occurred (Fig. 5.6.1) [3].

During 2013, 205 cases of mumps were reported. This is a considerable decline compared with the 397 cases reported in 2012 (Figure 5.6.1). In the second half of 2013, two outbreaks were identified in the north-west ('Noord-Holland') (n=80). The remaining mumps cases were spread throughout the country. Of all 205 reported cases in 2013, 59% were in males; the median age was 27 years (range 1-79 years). Fifty-five per cent were twice vaccinated, 9% once vaccinated, 23% unvaccinated and for 11% of them the vaccination status was unknown (Figure-5.6.2). In total, 8 cases were hospitalised due to mumps complications, no deaths were reported (Table 5.6.1).
Since 2012, the number of reported mumps cases among students has declined in the Netherlands. Conversely, there has been an increase in the number of mumps cases among non-students (>25 years of age) from non-university cities. This observed shift may be due to increased herd immunity among the student population. However, with continued enrolment of potentially susceptible students in university, the herd immunity among the student population may decline [3]. In October 2013, a cluster of mumps cases was observed in Volendam, a village with high MMR vaccination coverage. In December 2013, an outbreak investigation was initiated with a case-control study to assess risk factors for mumps. Analysis of this study is ongoing.

5.6.3 Pathogen

Since the start of nationwide mumps outbreaks in the Netherlands in late 2009, two major mumps virus genotype G strains have been identified based on the sequences of the small hydrophobic (SH) gene, named variant 1 (MuVs/Delft.NLD/03.10) and variant 2 (MuVs/Scheemda.NLD/12.10). Variant 1 was predominant during the first outbreak season (2009-2010), whereas variant 2 dominated the second and third outbreak seasons (2010-2012). Mumps virus variant 2 was associated with a higher risk of orchitis [4]. In 2013, most mumps patients were infected with mumps virus variant 1 (53 out of 70 sequenced virus strains; Figure 5.6.3), but on basis of sequencing of other mumps genes, significant differences were found between the recent variants and the original outbreak variant.

5.6.4 Research

5.6.4.1 Sequencing of mumps virus genes

The sequencing of additional mumps virus genes has shown that mumps virus genotype G variants 1 and 2 differ not only in the SH gene, but also in the haemagglutinin-neuraminidase (HN) gene and fusion (F) gene. Virological differences were also observed, including salivary viral load and detection of mumps virus in urine. These mumps virus strains are currently being studied in vitro to find possible differences in pathogenesis.

5.6.4.2 Immunity in vaccinated persons

Results from a study funded by ZonMW (2011, WP1.1) showed that mumps-specific IgG concentrations of vaccinated students sampled before the first mumps outbreaks in the Netherlands were generally lower in infected persons than in non-infected persons. However, no clear serological cut-off of immune protection could be established. Studies are ongoing with newly developed neutralisation assays to analyse the cross-protective potential of the vaccine-acquired immune response against the different genotype G wild type mumps virus strains that have circulated in the Netherlands in recent years.

5.6.4.3 Age-specific vaccine effectiveness

During a previous mumps outbreak between August 2007 and May 2009, a cross-sectional study in primary schoolchildren and their household members was conducted to estimate the vaccine effectiveness (VE) of the MMR vaccine against mumps [3]. Additionally, we analysed age-specific VE against mumps in the participants of this study. We used the self-reported vaccination status and occurrence of mumps as obtained from all household members through a questionnaire. The estimated VE was high among 1-4 year-olds (94.2%, 95% CI 76.2-98.6%) followed by a decrease among 5-8 year-olds (78.6%, 95% CI 48.9-91.1%). After the booster dose, in 9-12 year-olds the estimated VE increased again (92.9%, 95% 80.4-97.4%) and thereafter the VE declined with age (in 13-26 year-olds: 85.4%, 95% CI 15.4-97.5%). In conclusion, the VE against mumps was high but waned after the first dose, as it did after the booster dose as well.

5.6.5 International developments

Many studies have been performed regarding mumps phylogeny, including in the United States, United Kingdom and France [6, 7].
Serological studies have shown a poor correlation between assays that measure mumps-specific IgG concentrations and the neutralising capacity of these antibodies. Furthermore, the correlation between virus neutralising antibodies and immune protection may be quite poor. There is clearly a need for immunoassays that correlate better with neutralisation tests [8].
Cellular studies suggest that the dependence on serology to evaluate mumps vaccine-effectiveness may be overemphasised [9].
A spatial method developed through analysis of seroprevalence and vaccination coverage data in Belgium identified regions with mumps outbreak potentially associated with low vaccination coverage. The study also estimated that the effective reproduction number for mumps would increase over time in Belgium. The study stated that with mumps vaccination lower numbers of naturally acquired infections could lead to increased waning of vaccine-induced immunity. In turn, this will lead to an increase in the susceptible population and, upon future introduction of mumps, large mumps outbreaks are inevitable [10].
In 2012 and 2013, over 4,000 mumps cases were notified in Flanders, Belgium among vaccinated university students. A cohort study found that intense social mixing, possible waning vaccine-induced immunity and incomplete MMR vaccination may have contributed to the outbreak. The effectiveness of two doses of MMR vaccine compared with one dose of MMR vaccine was 68% (95% CI: -24-92%) [11].
In Ohio, in the United States, a mumps outbreak which began at a university in January 2014 has resulted in the largest mumps outbreak since 1979. To date, over 450 cases have been reported. Among the cases, 14 people were hospitalised due to mumps complications including orchitis, oophoritis and hearing loss (unpublished data – available from Columbus Public Health website http://columbus.gov/Templates/Detail.aspx?id=69188).

5.6.6 Tables and figures

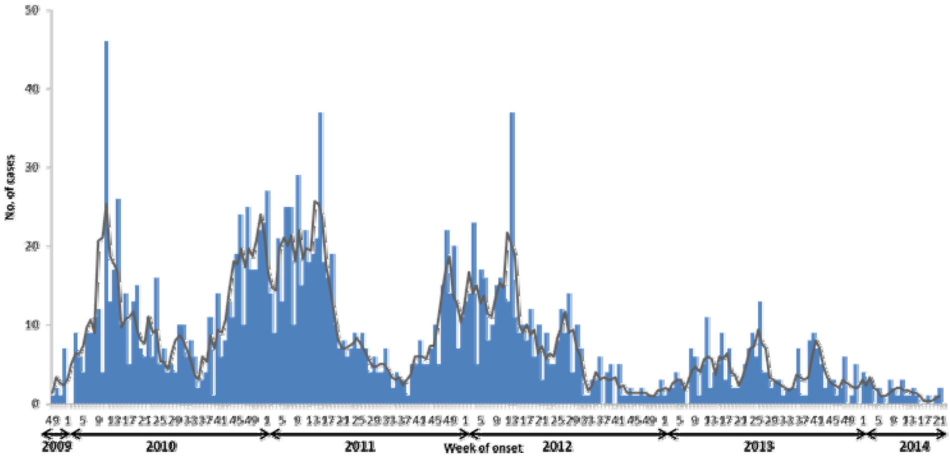

Figure 5.6.1 Number of notified mumps cases by week of onset, 01/12/2009 – 01/06/2014 (n=1817); black line indicates a 3-week moving average.

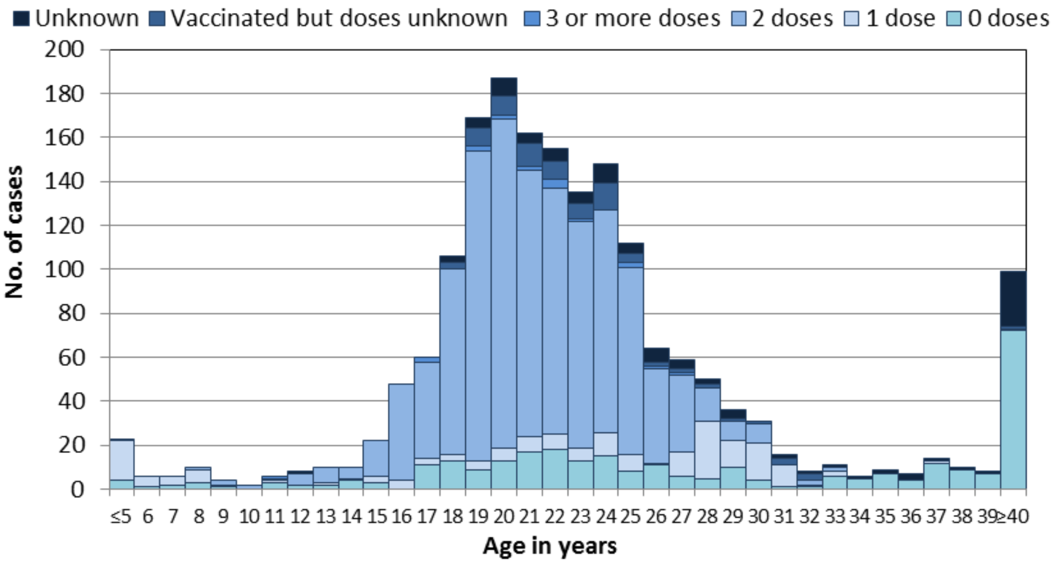

Figure 5.6.2 Number of notified mumps cases by age and vaccinations status, 01/12/2009 – 01/06/2014 (n=1817)

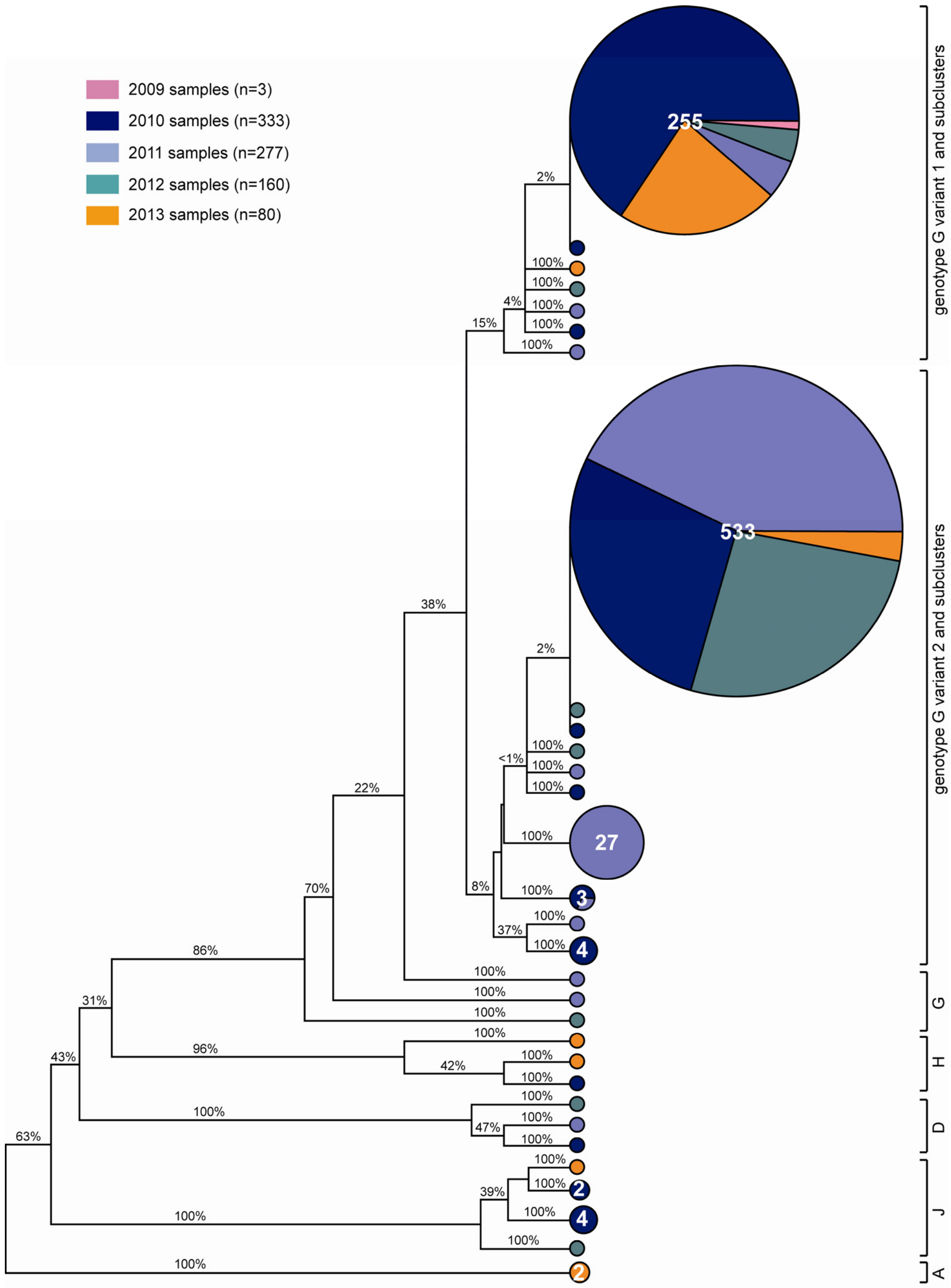

Figure 5.6.3 UPGMA tree based on the small hydrophobic (SH) gene sequences of 853 mumps viruses.

Percentages indicate the bootstrap values (1,000 replicates). Colours represent the year of sampling. The number of persons per cluster is shown in white. Behind each cluster the genotype is indicated.

Table 5.6.1 Reported complications among 1,817 cases of mumps notified between 01/12/2009 and 01/06/2014 (n=146)

Complications	**Number of reported cases**	**%**
Orchitis	124	11.7 (men)
Oophoritis	0	0 (women)
Meningitis	3	0.17
Orchitis & Meningitis	3	0.3 (men)
Encephalitis	0	0
Pancreatitis	2	0.11
Meningitis, Encephalitis & Pancreatitis	1	0.06
Tyreoiditis	1	0.06
Deafness	3	0.17
Other	9	0.50

5.6.7 *Literature*

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5.7 Measles

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

5.7.1 Key points

- Between May 2013 and February 2014, a large outbreak of measles occurred mainly among unvaccinated primary school aged children in low vaccination coverage areas ('Bible Belt'); in total, 2,640 cases were reported, which included 182 hospitalisations and one death.
- The main outbreak control intervention was to recommend early MMR vaccination for infants aged 6-14 months in 29 municipalities with a vaccination coverage <90%. RIVM provided weekly online updates of the outbreak and advice for the protection of health care workers against measles.
- Before the large outbreak, a significant increase in the notification rate of measles occurred early in 2013. One of the reported measles clusters included health care workers and children not yet vaccinated against measles.

5.7.2 Epidemiology

In February/March 2013, five clusters of measles were reported, four of which could be linked to the import of the infection from abroad. A description of these can be found in the 2013 NIP report [1]. These five clusters consisted of 20 cases. In addition, two solitary cases (both imported) were reported. The largest cluster consisted of 9 persons and started with a case involving an incompletely vaccinated general practitioner (GP) and her child. Subsequently, several other children and adults developed measles (Den Haag cluster). The measles virus had been imported from Italy and was the "Taunton" type of genotype D8, which was highly prevalent in Europe early in 2013. Of the six adult cases in this cluster with known vaccination status, four were vaccinated (1 dose (1), 2 doses (2), 3 doses (1)). This high vaccination coverage among cases does not necessarily indicate a low vaccine-effectiveness, as a high number of vaccinated persons were likely exposed to measles here. The relative proportion of cases occurring in vaccinated individuals increases as the vaccine coverage of the exposed population is high [2]. The second cluster consisted of 4 persons with measles within an orthodox-reformed family of which the children were attending a school with low vaccination coverage (March 2013). There were no other cases reported related to this cluster. The genotype D8 virus identified was different from the Den Haag cluster.

5.7.2.1 Measles outbreak 2013

In May 2013, a large epidemic began among unvaccinated orthodox Protestants, with initial cases mainly reported by GGD Zuid Holland Zuid and Rivierenland [3, 4]. The source of infection of the index case remains unknown. Molecular typing of the outbreak strain showed it had the same D8 sequence type "Taunton" as the Den Haag cluster, but a direct epidemiological link between the two clusters is highly unlikely as the last reported case in the Den Haag outbreak had a date of onset of 25 February 2014.

Between 1/5/2013 and 26/2/2014, 2,640 cases were reported (Figures 5.7.1 and 5.7.2). The outbreak in areas with higher vaccination coverage lagged behind the outbreak in the low vaccination coverage areas. In both, a clear effect of the school holidays was seen (Figure 5.7.1).
Of all reported cases, 94% were unvaccinated, 5% were vaccinated once and 1% were vaccinated at least twice (1% vaccination status unknown). Most cases (56%) were aged 4-12 years (Figure 5.7.3). A total 182 cases were hospitalised. None of these people were fully vaccinated. One death was reported in an unvaccinated 17-year-old female who had an underlying illness. The outbreak was expected based on low seroprevalence among orthodox Protestant children born after the 1999-2000 outbreak [5]. Several importations into Canada were reported, two of which led to outbreaks in Alberta and British Columbia. One of these included six cases in the US.
The outbreak response consisted of an early MMR vaccination for infants aged 6-14 months in 29 municipalities with vaccine coverage <90%, catch-up vaccinations for all individuals up to 19 years of age, and advice to vaccinate health care workers (for further details, see NIP report 2013) [1]. Regarding the early MMR vaccination: for infants ages 6-12 months, this meant an extra MMR (MMR-0), for children ages 14 months and younger, the MMR-1 was brought forward.

5.7.3 *Pathogen*

Most measles cases genotyped in 2013 by RIVM were of genotype D8, but there were different sequence types identified, pointing to separate introductions for each of the different types rather than endemic circulation. The major D8 sequence type "Taunton" caused the outbreak in The Hague and the large Bible Belt outbreak. In 2013, this type had the highest prevalence within Europe (WHO/EURO Labnet measles/rubella meeting report, Helsinki, May 2014). In addition, there were three imported cases with a different genotype.

5.7.4 *Research*

Measles research conducted during 2013 was largely focussed on the outbreak. Several themes were being addressed and incorporated in different research and study outlines:
- Evaluation of impact and effects of early MMR vaccination;
- Assessment of serological correlates for protection;
- Underreporting;
- Validity of measles antibody screening of personnel in the health care setting;
- Implementation of advice for protection of health care workers;
- Environmental surveillance for measles;
- Societal costs of the measles outbreak.

To date, and on basis of the preliminary outcome of some these studies, it has been tentatively concluded that early MMR immunisation did indeed result in lower attack rates of measles among the vaccinated children. More results are expected in the coming year.

5.7.5 *International developments*

During 2013, 31,520 measles cases were reported by 50 countries in the WHO European Region. Of these, 96% were reported by nine countries: Georgia (7,830), Germany (1,773), Italy (2,216), the Netherlands (2,499), Romania (1,074), the Russian Federation (2,174), Turkey (7,404), Ukraine (3,308) and the United Kingdom (1,900). The highest incidence per million inhabitants for

2013 was reported in Georgia (1,803.8) followed by the Netherlands (149.1). Most measles cases (75%) occurred among unvaccinated persons and 34% were age 20 years and older [5].

Recently an outbreak of measles was described in which a first example of a twice vaccinated individual was illustrated who transmitted the virus to four contacts [6]. This outbreak raises the question of whether the waning of vaccine-induced immunity will threaten the elimination of measles. The observation that during the recent Bible Belt outbreak relatively few twice vaccinated individuals were infected is reassuring, considering nearly 200 cases of measles were admitted to hospital and hence many twice vaccinated health care workers will have been exposed. Also reassuring is the fact that the PIENTER-2 study showed that the waning of antibody concentrations after the second MMR vaccination was slow, indicating long-lasting immunological memory [4]. The enhanced surveillance and study of vaccine failures will be crucial to assessing the duration of vaccine-induced immunity.

5.7.6 *Tables and figures*

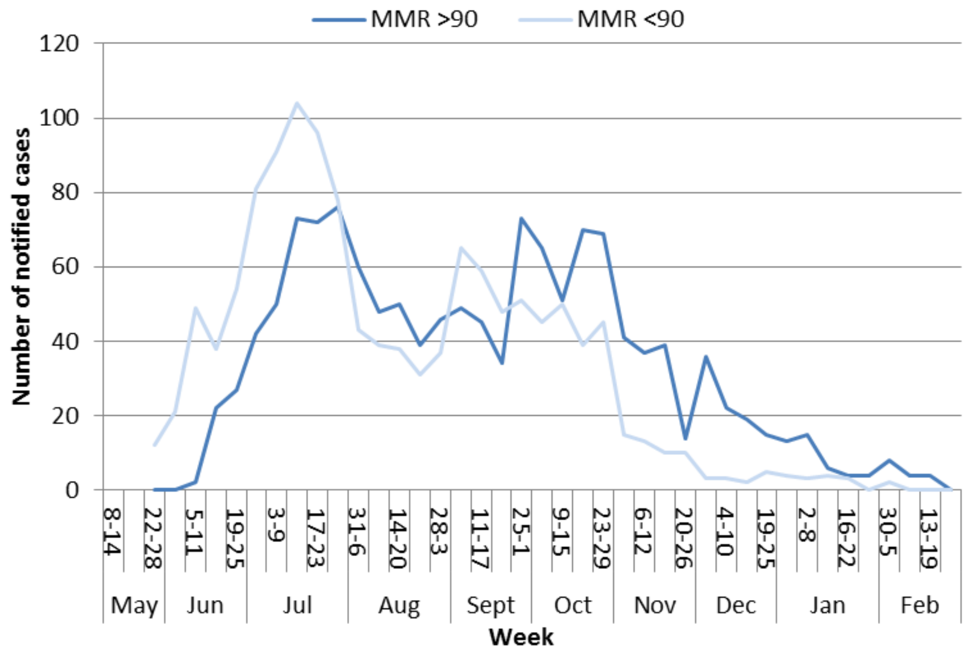

Figure 5.7.1 Reported measles cases by week of rash onset and Municipal Health Service region (< and >90% MMR coverage; n=2640), 1-5-2013 to 26-2-2014*
*Imported cases (n=29) are not included. In the figure, 4 cases are not included because their date of onset was missing.

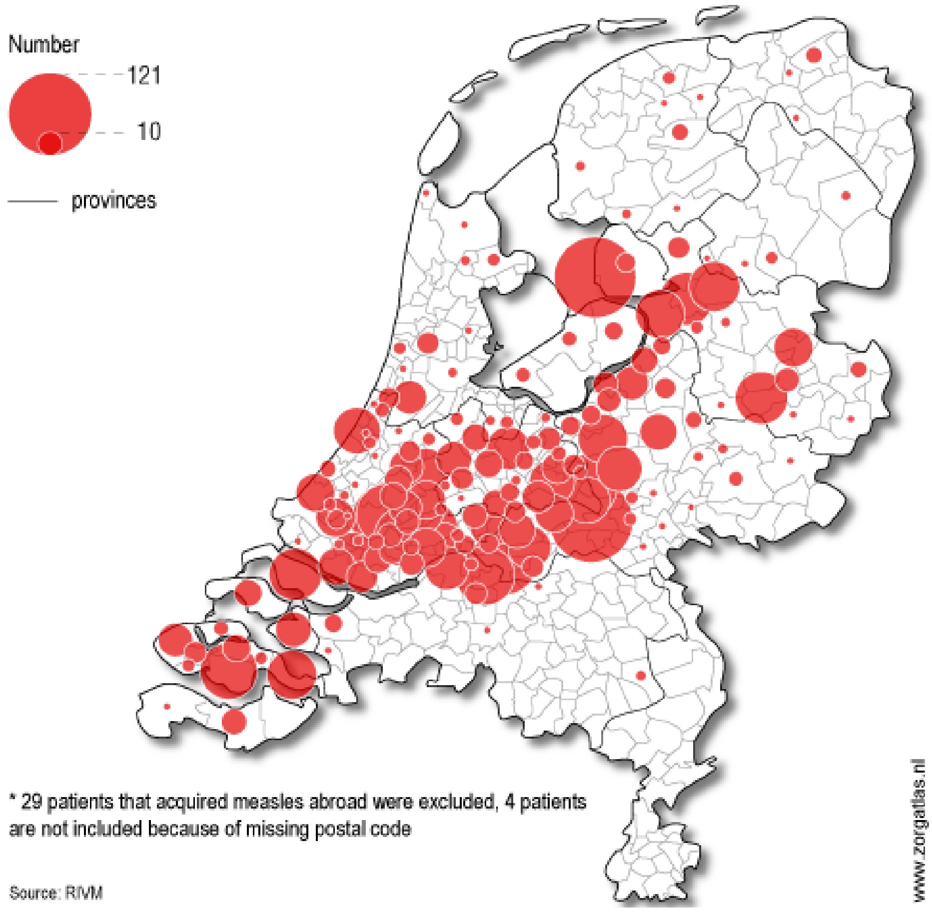

Figure 5.7.2 Measles incidence (reported measles cases per 100,000 population) by municipality (n=2640), 1-5-2013 to 26-2-2014*
*Imported cases (n=29) are not included. In the figure, 4 cases are not included since information on municipality was not provided.

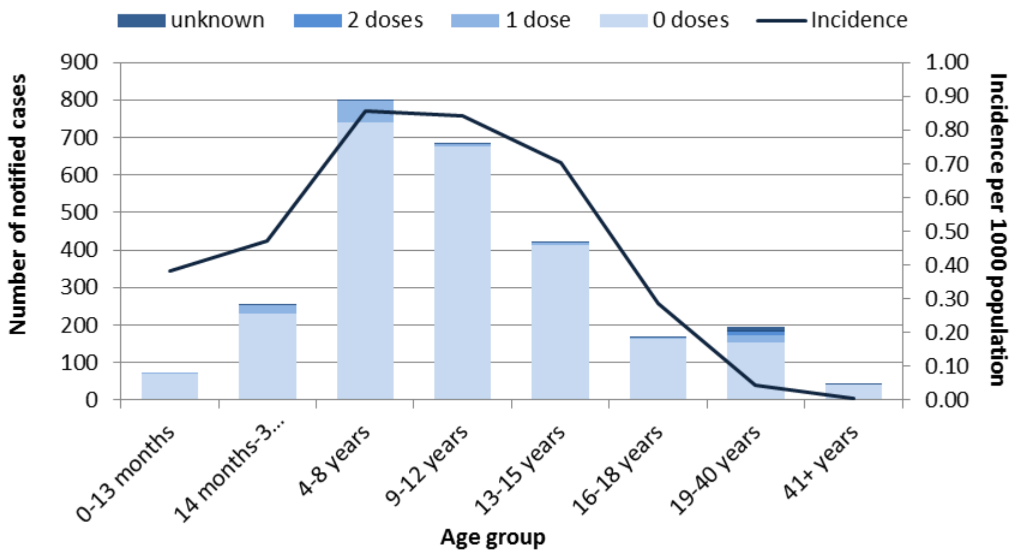

Figure 5.7.3 Reported measles cases by age group and vaccination status (n=2640), 1-5-2013 to 26-2-2014

5.7.7 Literature

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5.8 Rubella

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

5.8.1 Key points

- During the first weeks of the measles epidemic in June 2013, a large but restricted rubella outbreak was identified at an orthodox reformed school with low vaccine coverage for religious reasons in the region ‘Hollands Midden’ in which 54 related cases were reported. This is the largest rubella outbreak in the Netherlands since 2004-2005.
- In 2013, a large rubella outbreak occurred in Poland. Three solitary cases with links to Poland were reported in the Netherlands in 2013, one of which could be partially genotyped (genotype 2B).

5.8.2 Epidemiology

During 2013, 57 cases of rubella were reported (incidence: 3.4/million population). Three of these cases were in adults, all of whom had a link to Poland. In total, 53 cases were linked to an orthodox reformed primary school (52 children and one parent). This outbreak occurred between mid-June and mid-July 2013. The median age of the cases was 7 years. The remaining case had an unknown source but was reported by the same MHS (GGD Hollands Midden). None of the the 54 outbreak cases was reported to have been vaccinated against rubella, but the vaccination status was unknown for 39 of them (72%).

5.8.3 *Pathogen*

One of the three cases linked to the outbreak in Poland could only partially be sequenced, which is related to low RNA concentrations detected in the clinical sample. The genotype, however, could be identified on the basis of a 525bp window, largely 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 the one identified for the Polish rubella case, 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).

5.8.4 *Research*

In 2014, rubella seroprevalence results from the PIENTER-2 study (2006/7) were published [1]. Overall seroprevalence was high (95%). Higher levels of rubella-specific antibodies were observed in the naturally infected cohorts than were in vaccinated cohorts. There was no evidence of important waning of vaccine-induced immunity. In the orthodox protestant group, individuals younger than 6 years of age were at risk for an infection with rubella, consistent with the school outbreak described above.

5.8.5 *International developments*

In 2013, a large rubella outbreak started in Poland. The outbreak is ongoing, with over 900 reported cases in March 2014 [2]. The vast majority of these cases are in adolescent males, reflecting the history of immunisation in Poland (selective vaccination of adolescent girls since 1989, universal two-dose MMR vaccination since 2004).

5.8.6 *Literature*

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5.9 Meningococcal serogroup C disease

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

5.9.1 *Key points*

- In 2013, six cases of meningococcal group C disease were reported. All cases were unvaccinated. The incidence of meningococcal serogroup C (MenC) disease has decreased enormously since the introduction of vaccination in 2002 to 0.04 per 100,000 in 2013.
- In the UK and in other countries an adolescent booster dose of MenC or MenACYW was implemented or recommended.

5.9.2 *Epidemiology*

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 decreased enormously (Figure 5.9.1). In 2013, six cases of invasive meningococcal group C disease were reported: three unvaccinated females of ages 1, 77 and 90 years, three unvaccinated males, one from Poland who was 28 years of age and two from the Netherlands who were 44 and 68 years old (Table 5.9.1). The 77 year-old woman died.

5.9.3 *Pathogen*

The incidence of invasive serogroup C meningococcal disease declined in all clonal complexes after the introduction of the MenC vaccine. The decline was most pronounced in clonal complex ST11 and ST8 [1]. It was previously observed that meningococci of these clonal complexes have a high frequency of capsule expression during nasopharyngeal colonisation [2].

5.9.4 *Research*

An intervention study (JIM-study - NTR4430) has started 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 14 months (10 and 12 year groups) and at 3 years during the mass campaign (15 year group). We will be able to compare the responses in this study with the immune response after a monovalent MenC-TT conjugate booster vaccination. The samples prior to and one month after vaccination have already been collected and, in the spring of 2015, the samples taken one year after vaccination will be collected.

5.9.5 *International developments*

In the UK, an adolescent booster vaccination (MenC) was implemented in 2014 for 13-14 year-olds to make the overall MenC immunisation programme more effective and to offer better protection in teenagers and young adults. Note, the UK's primary vaccination schedule for MenC was changed (2013) by removing the second dose at 4 months, but sustaining the first booster at 12-13 months. From mid-August 2014, a catch-up programme of limited duration – possibly up to five years – has been organised to offer the vaccine for the first time to university entrants under the age of 25 years, i.e. those who will not have been vaccinated at 14 years of age under the revised schedule. The UK Joint Committee on Vaccination and Immunisation (JCVI) noted that older adolescents, who will be older than the age of the routine booster at the time of the introduction of the adolescent booster programme, which will start in the 2013/14 academic year, may have only received a single dose of MenC vaccine before twelve months of age. This group might be at increased risk of contracting MenC disease if they go to a university setting for the first time and should be offered a single dose of MenC vaccine. This is because the disease can spread quickly in areas where people live close to each other, e.g. in universities or other shared accommodation.
(https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/197618/MenC_letter_FINAL.pdf).

Various countries (e.g. Austria, the Czech Republic, Poland and Greece) recommend the quadrivalent meningococcal serogroup ACWY conjugate vaccine for booster vaccination of adolescents in order to keep the carriage rate low and to enlarge the meningococcal serogroup protection beyond MenC [3].

Read et al. [4] have performed a phase 3 carriage study into English university students with MenACWY-CRM vaccine. About 3,000 students at 10 universities across England were enrolled from September to December 2010 to receive one dose of MenACWY-CRM vaccine (n=956) or other vaccines. Across the cumulative time points after one year, MenACWY-CRM vaccination was associated with a carriage reduction of 32.7% against serogroup ACWY strains.

5.9.6 *Tables and figures*

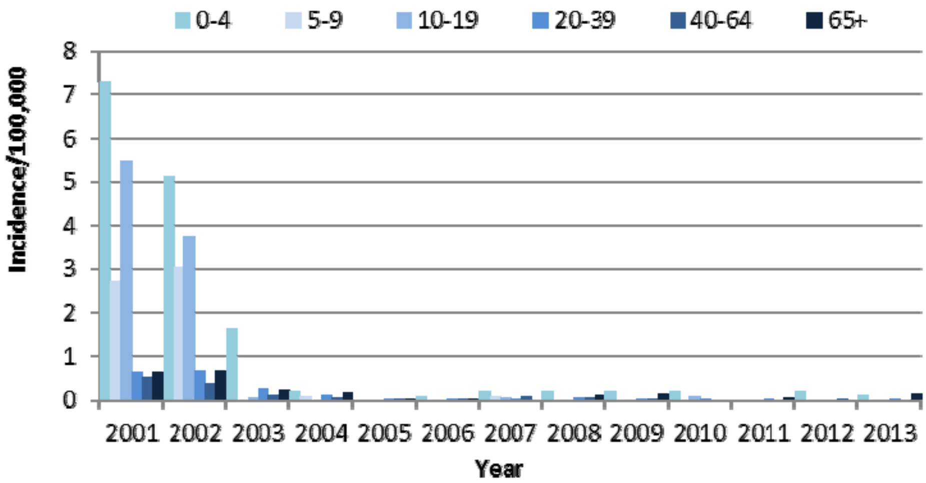

Figure 5.9.1 Age-specific incidence of meningococcal C disease (cerebrospinal fluid and blood isolates), 2001-2013

Table 5.9.1 Absolute numbers of invasive meningococcal C isolates, 2001-2013

Age in yrs	**'01**	**'02**	**'03**	**'04**	**'05**	**'06**	**'07**	**'08**	**'09**	**'10**	**'11**	**'12**	**'13**
0-4	73	52	17	2	0	1	2	2	2	2	0	2	1
5-9	27	30	0	1	0	0	1	0	0	0	0	0	0
10-19	105	73	1	0	0	0	1	0	0	2	0	0	0
20-39	31	32	12	6	1	1	1	3	2	2	1	0	1
40-64	27	20	7	4	2	1	5	3	1	0	0	1	0
65+	14	15	5	4	1	1	0	3	4	0	2	0	4
Total	277	222	42	17	4	4	10	11	9	6	3	3	6

5.9.7 *Literature*

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Infectious Diseases; May 28- June 1, 2013; Milan Abstract A-534-0044-01472; 2013.

5.10 Hepatitis B

S. Hahné, S. Hofstraat, L. Soetens, B. van Benthem, J. Cremer, A. Suijkerbuijk, K. Benschop, A.J. King

5.10.1 Key points

- In 2013, the incidence of acute hepatitis B infection (HBV) notifications was 0.8 per 100,000 population. Since notification started, it has not been this low.
- A relatively high incidence was reported in the North-East of the country.
- Male homosexual contact remained the most frequently reported risk factor.
- Molecular surveillance suggests ongoing transmission of a genotype A strain.
- Recent literature reports suggest that screening of migrants for HBV is likely to be cost- effective.

5.10.2 Epidemiology

In 2013, 1,254 cases of hepatitis B virus (HBV) infection were notified (data up to March 2014). Of these, 1,109 (88%) were chronic infections and 130 (10%) were acute infections. For 15 cases, the status of infection was unknown. Compared with 2012 (171 cases), the number of notified acute HBV infections decreased. The incidence of acute HBV notifications in 2013 was 0.8 per 100,000 population (2012: 1.0/100,000), 1.2/100,000 among men and 0.4/100,000 among women. The HBV incidence, which has been decreasing for men and women since 2004, seems to have stabilised for women but continues to decrease for men (Figure 5.10.1).
In 2013, most cases of acute HBV infection (62%) were acquired through sexual contact. Nine percent were acquired through other routes. For 29% of reports of acute HBV infection, the most likely route of transmission remained unknown, despite source tracing. Among men (99 cases), sexual contacts between men who have sex with men (MSM) accounted for 36% of acute infections (n=36) and heterosexual transmission for 22%. Among women (31 cases), heterosexual contact accounted for 71% (n=22) of cases.

5.10.2.1 Chronic HBV epidemiology

In 2013, most cases of chronic HBV infection (57%) were acquired through vertical transmission. Five per cent were infected through sexual contact and for 27% of the reports of chronic HBV infection the most likely route of transmission was unknown. Eighty-three per cent of the chronic HBV patients were born abroad (with Turkey, China and Somalia as most frequently reported countries of birth for 30% of chronic cases).

5.10.3 Pathogen

The molecular sequencing and typing of acute HBV cases continued in 2013. In total, 93 samples of acute cases were available for genotyping. PCR amplification and sequencing gave results for 84 (90%) samples for the S-region. A minimum spanning tree on the basis of S-region sequences is shown in Figure 5.10.2. This shows that the largest cluster of cases (n=28) continues to be among genotype A male cases.

5.10.4 *Research*

The molecular typing of notified acute HBV cases and of chronic HBV cases in the target groups for selective vaccination has continued in 2014.
An enhanced analysis of epidemiological and phylogenetic surveillance data of acute HBV notifications between 2009-2013 is being finalised (Soetens et al). This identified two spatio-geographic clusters (South West, 2009-2010) and North-East (2010-2013) and an increased incidence in the eastern Dutch border areas. The relation with vaccine uptake among MSM is being studied.
Currently the RIVM-CIb is working on implementing the molecular platform VIRO-TypeNed [1] to aid molecular surveillance of HBV, as well as HAV and HCV. The platform combines molecular data with epidemiological and transmission data to allow for a more in-depth surveillance of HBV, source monitoring and detect antiviral resistance and immune escape variants.
A recent RIVM-led study found that prophylactic paracetamol treatment during vaccination has a negative influence on the antibody concentration after hepatitis B vaccination in adults. These findings prompt us to consider therapeutic instead of prophylactic treatment to ensure maximal vaccination efficacy and to retain the possibility of treating pain and fever after vaccination [2].

5.10.5 *International developments*

The EU funded international project EUHepscreen was started at the end of 2011 and will continue 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 (www.hepscreen.eu).
In a recent publication, Rossi et al. performed a cost-effective analysis to compare four HBV screening and vaccination strategies with no intervention in a hypothetical cohort of newly-arriving adult Canadian immigrants [3]. Screening for chronic HBV infection, and offering treatment if indicated, was found to be the most cost-effective intervention (cost estimate 40,880 Canadian dollars/QALY gained, relative to no intervention). This finding is consistent with other literature [4]. The planned Health Council’s assessment of HBV and HCV screening of migrants is therefore an urgent priority.

5.10.6 *Tables and figures*

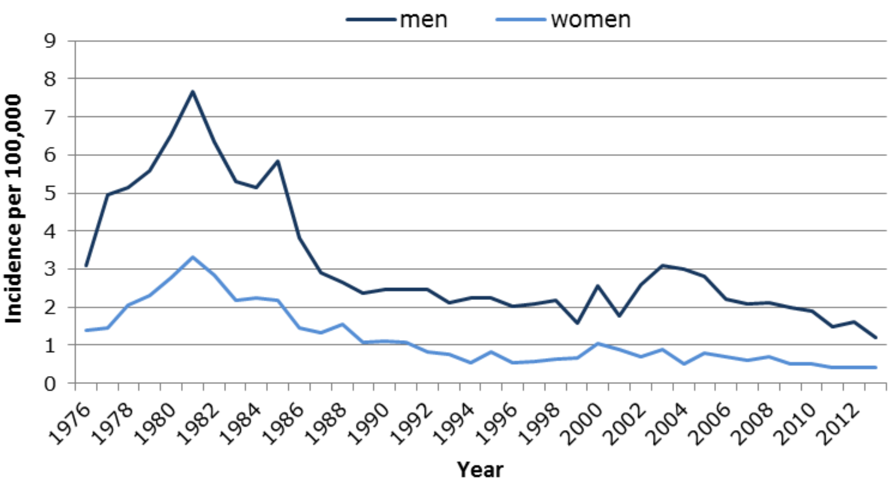

Figure 5.10.1 Incidence of notified acute HBV infections among men and women, the Netherlands, 1976-2013 (Source: Osiris/IGZ database)

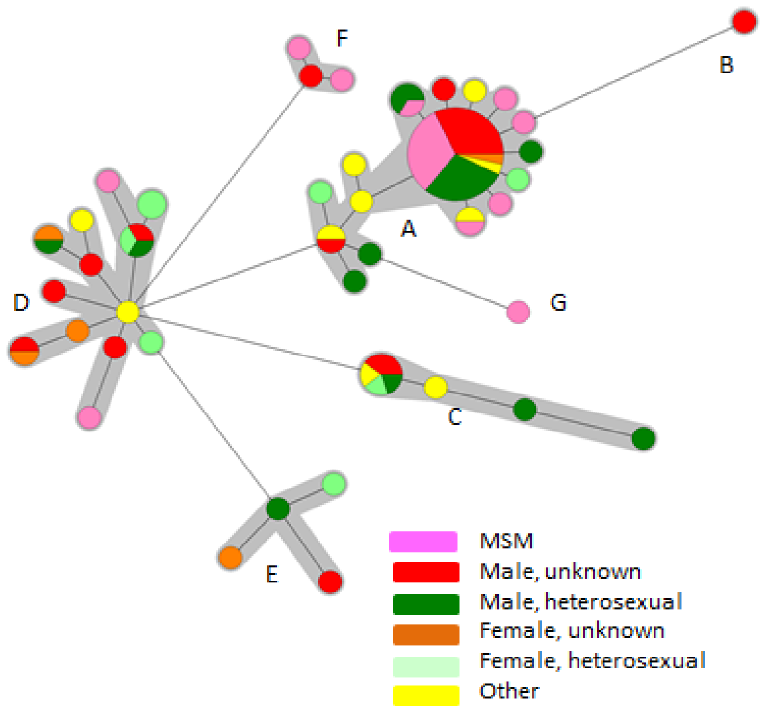

Figure 5.10.2 Minimum spanning tree based on the S-region sequence of acute HBV cases in 2013 by reported risk factor (n=84)

5.10.7 *Literature*

1. Niesters HG, Rossen JW, van der Avoort H, Baas D, Benschop K, Claas EC, et al. Laboratory-based surveillance in the molecular era: the TYPENED model, a joint data-sharing platform for clinical and public health laboratories. Euro surveillance: bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2013;18(4):20387.
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5.11 **Pneumococcal disease**

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5.11.1 *Key points*

- Introduction of 7-valent pneumococcal conjugate vaccination (PCV7) in 2006 led to a major decrease in vaccine-type invasive pneumococcal disease (IPD)

from 7.4 per 100,000 per year in 2004-2006 to less than 1 per 100,000 per year in 2012-2014.
- Introduction of PCV10 in 2011 reduced the number of IPD cases caused by the additional PCV10 serotypes (1, 5 and 7F) in the vaccinated age groups.
- Longer follow-up is needed to assess the impact of PCV10 introduction in unvaccinated age groups.
- The incidence of non-vaccine-type invasive pneumococcal disease (IPD) increased after introduction of PCV7, but this increase was less pronounced in 2012-2014 in all age groups.
- The incidence of mortality due to IPD decreased from 2.4 per 100,000 per year in 2004-2006 to 1.7 per 100,000 per year in 2008-2012.
- The vaccination schedule was changed from 3+1 to 2+1 (at 2, 4 and 11 months of age) in November 2013.

5.11.2 Epidemiology

5.11.2.1 Change of vaccination schedule

In 2006, 7-valent pneumococcal conjugate vaccination (PCV7; including serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) was introduced in the NIP for children born on or after April 1, 2006. In 2011, PCV7 was replaced by PCV10 (with additional serotypes 1, 5 and 7F) for children born on or after March 1, 2011. The vaccination schedule changed from four to three doses of PCV10, given at 2, 4 and 11 months of age, in November 2013, because of established herd immunity after introduction of PCV7 (http://www.gezondheidsraad.nl/sites/default/files/201328_Vaccinatie_zuigelingen_tegen_pneumokokkeninfecties_3.pdf).

5.11.2.2 Vaccine type IPD

In the last 2 years (period June 2012-May 2014), the incidence of IPD caused by PCV7 serotypes decreased to less than 1 per 100,000 per year, indicating a large effect of PCV7 introduction in vaccinated and unvaccinated age groups (Figure 5.11.1). Introduction of PCV10 in 2011 decreased the incidence of IPD caused by the three additional serotypes in PCV10 in vaccinated age groups. For example, there were 0 cases of serotype 1, 5 and 7F in the <2 years of age group in the last 2 years in the sentinel surveillance (Figure 5.11.2). In the nationwide surveillance, as well, the number of cases in <2 year-olds clearly decreased after 2011 with 0 cases of serotype 1, 5 and 7F from January to May 2014 (Figure 5.11.3). Furthermore, we compared a PCV10-eligible birth cohort with a PCV7-eligible birth cohort using national surveillance data and observed a highly significant decrease in the incidence rate of IPD caused by the additional PCV10 serotypes (incidence rate ratio = 0.06; 95% confidence interval: 0.01-0.42) [1]. Figure 5.11.2 also shows a decrease in the incidence of IPD caused by the additional PCV10 serotypes in the 50-64 and 65+ age groups in 2012-2014 compared with 2010-2012. This may indicate herd effects as a result of PCV10 introduction. However, longer follow-up is needed to discern herd effects from temporal changes in IPD incidence.

5.11.2.3 Non-vaccine type IPD

After the introduction of PCV7, the incidence of IPD caused by non-vaccine serotypes increased, especially in the older age groups (Figure 5.11.4 shows the increase in non-PCV10 serotype IPD). In the last 2 years, there was no large increase anymore of non-vaccine type IPD. This was partly due to a decrease in serotype 19A IPD. It is unknown whether this is a vaccine effect (through cross-protection) or natural fluctuation. Longer follow-up is needed to assess this.

5.11.2.4 Overall IPD

Overall, IPD incidence clearly decreased in the major affected age groups of children <5 years and elderly of 65 years and older (Figure 5.11.5).

5.11.2.5 Mortality of IPD

Clinical IPD surveillance showed that the case fatality rate of IPD significantly decreased from 16% in 2004-2006 to 12% in 2008-2012. The incidence of mortality due to IPD significantly decreased from 2.4 per 100,000 per year in 2004-2006 to 1.7 per 100,000 per year in 2008-2012. Case fatality rate and mortality incidence were highest among patients 65 years or older (17% and 8.3/100,000 respectively in 2008-2012).

5.11.2.6 Vaccine failure

Since the introduction of PCV7, there have been 40 cases of vaccine-type IPD among vaccine-eligible children in the nationwide surveillance. Of these, 13 children (32.5%) were vaccinated with at least 2 doses (Table 5.11.1). Six of these children had serotype 19F IPD.

5.11.3 Pathogen

Small changes in the characteristics of the pneumococcal strains isolated from IPD patients have been observed. Genetic diversity in upcoming serotypes, such as serotype 22F and 12F, increased in 2010-2012 compared with previous years. In 2010-2012, two strains (of 988 tested; 0.2%) switched a non-vaccine capsule for another non-vaccine capsule, while in 2008-2009 five strains (of 1447 tested; 0.3%) switched both non-vaccine and vaccine capsules.

5.11.4 Research

5.11.4.1 Antibody responses

To assess temporal changes, we compared antibody levels against 13 pneumococcal serotypes between 1995-1996 (PIENTER-1 data) and 2006-2007 (PIENTER-2 data) in unvaccinated individuals of ages 0 to 79 years [2]. The antibody levels were significantly higher in 2006-2007 for serotypes 1, 6A, 6B, 9V, 18C, 19A, 19F and 23F and lower for serotype 3. This indicates that the level of pneumococcal antibodies is dynamic and not only influenced by vaccination.
In children 0-3 years, the determinants of higher pneumococcal antibody levels using PIENTER-2 data (2006-2007) were larger household size, increasing age and living in a high vaccination coverage area (children eligible for vaccination based on birth of date were excluded) [3]. In participants, ages 65 years or older, male gender and lower level of education were determinants of higher pneumococcal antibody levels.

5.11.4.2 Pneumococcal carriage

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, carriage of vaccine-type pneumococci almost completely disappeared (1%), but overall pneumococcal carriage was similar to the pre-vaccination carriage rates (55%). Distribution of the carriage of non-vaccine serotypes was more similar to pre-PCV7 data with none of the serotypes having a carriage rate above 10%, suggesting a new balance in non-vaccine serotypes. Whereas an increase in carriage rates of 19A was seen in 2010 (13% vs 2%), 19A carriage rates declined again in 2012/13 in PCV7 vaccinated children (8%) as well as in PCV10 vaccinated children (9%) [4].

5.11.5 *International developments*

The results of the CAPITA study (Community-Acquired Pneumonia Immunization Trial in Adults) were presented at the ISPPD 2014 (International Symposium on Pneumococci and Pneumococcal Diseases). This randomized placebo-controlled trial, with approximately 85,000 participants, showed that PCV13 significantly decreased vaccine-type community-acquired pneumonia (CAP) with 46% in adults ages 65 years or older. Vaccine-type IPD was significantly reduced with 75%.
Vemer et al. calculated the cost-effectiveness of infant pneumococcal vaccination in the Netherlands, comparing PCV13 with currently used PCV10 [5]. Taking only direct effects on IPD into account, PCV13 was not found to be cost-effective, at a price difference with PCV10 of €11 per dose. If herd effects, serotype replacement and non-invasive disease were taken into account, the incremental cost-effectiveness ratio of PCV13 compared with PCV10 was below €30,000 per quality adjusted life year gained in most scenarios. Assuming a price difference below €2.63, PCV13 was considered to be the dominant vaccination strategy.

5.11.6 *Tables and figures*

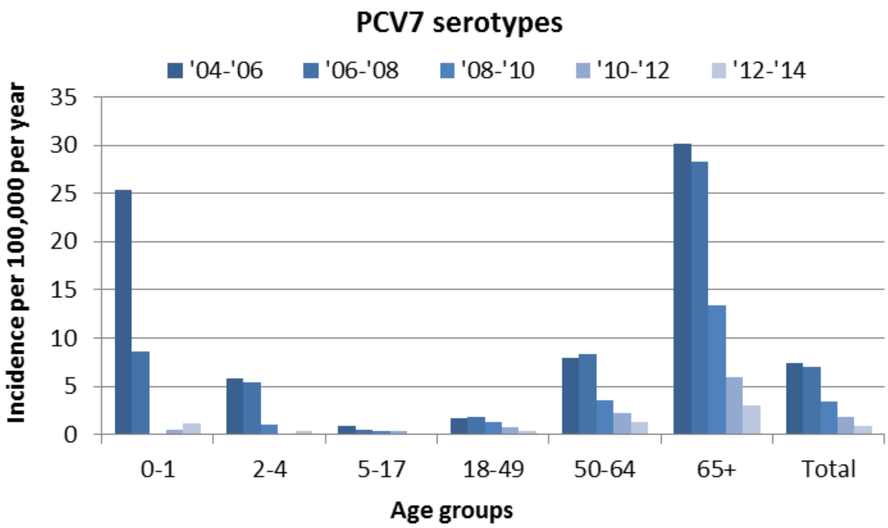

Figure 5.11.1 Incidence of IPD caused by PCV7 serotypes, presented by age group and time period ('04-'06 = June 2004-May 2006, '06-'08 = June 2006-May 2008, etc.). PCV7 was introduced in June 2006 and PCV10 in May 2011. Data of sentinel surveillance are used and extrapolated to the Dutch population.

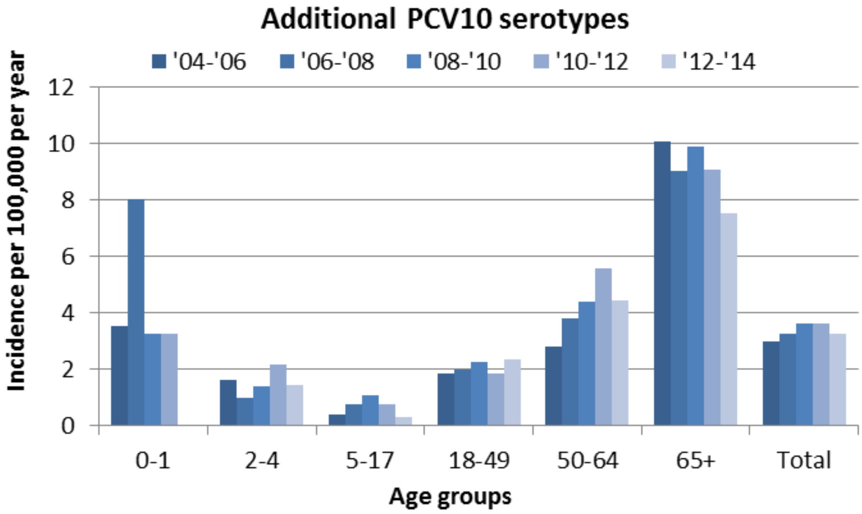

Figure 5.11.2 Incidence of IPD caused by additional PCV10 serotypes (1, 5 and 7F), presented by age group and time period ('04-'06 = June 2004 - May 2006, '06-'08 = June 2006 - May 2008, etc.). PCV7 was introduced in June 2006 and PCV10 in May 2011. Data from sentinel surveillance are used and extrapolated to the Dutch population.

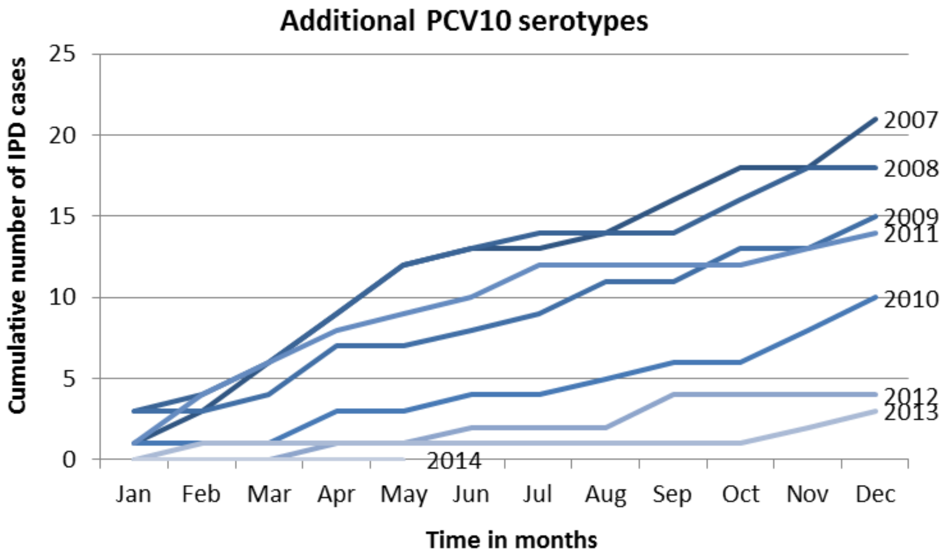

Figure 5.11.3 Cumulative number of IPD cases caused by the additional PCV10 serotypes (1, 5 and 7F) in children < 2 years of age. PCV10 was introduced in May 2011. Data from nationwide surveillance are used.

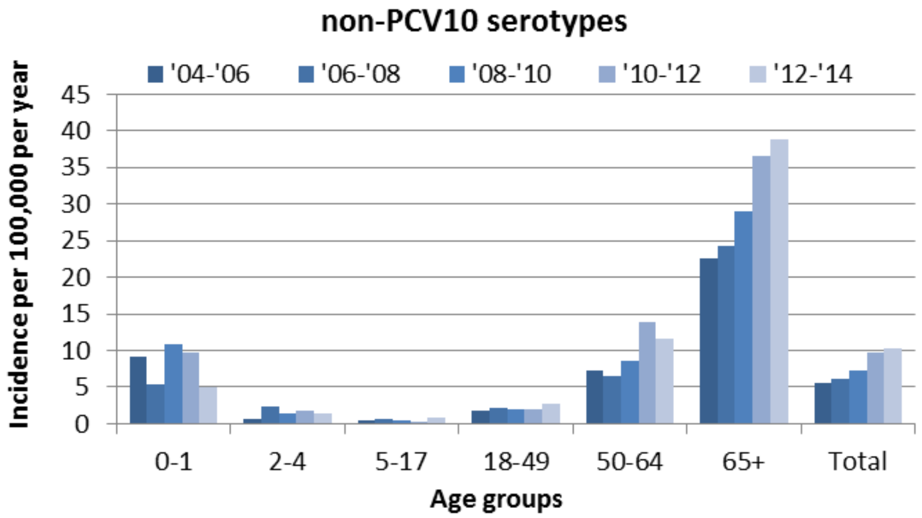

Figure 5.11.4 Incidence of IPD caused by non-PCV10 serotypes, presented by age group and time period ('04-'06 = June 2004-May 2006, '06-'08 = June 2006-May 2008, etc.). PCV7 was introduced in June 2006 and PCV10 in May 2011. Data from sentinel surveillance are used and extrapolated to the Dutch population.

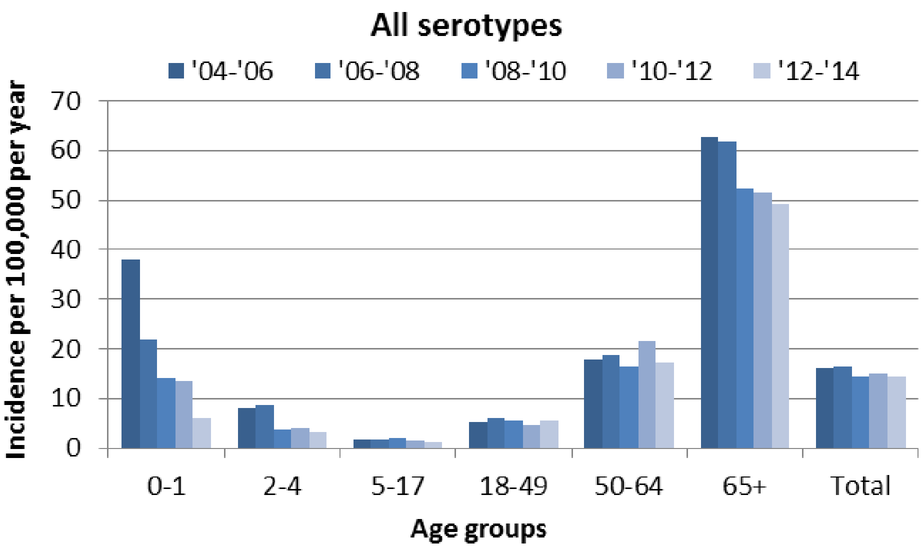

Figure 5.11.5 The incidence of IPD caused by all serotypes, presented by age group and time period ('04-'06 = June 2004-May 2006, '06-'08 = June 2006-May 2008, etc.). PCV7 was introduced in June 2006 and PCV10 in May 2011. Data from sentinel surveillance are used and extrapolated to the Dutch population.

Table 5.11.1 Children with vaccine type IPD who received at least two vaccinations based on nationwide surveillance data

Year of diagnosis	Age in months	Serotype	Vaccine received	Number of vaccinations	Patient details if known
2008	3	9V	PCV7	2	Diagnosis within 1 wk after 2nd dose
2008	3	6B	PCV7	2	Diagnosis at least 2 wks after 2nd dose
2008	7	6B	PCV7	3	?
2009	29	19F	PCV7	4	?
2009	6	19F	PCV7	3	-
2010	12	6B	PCV7	4	?
2011	59	19F	PCV7	4	Nephrotic syndrome
2012	63	18C	PCV7	4	-
2012	45	19F	PCV7	4	Leukemia
2012	54	9V	PCV7	4	?
2013	2	7F	PCV10	2	Premature, diagnosis within 1 wk after 2nd dose
2013	73	19F	PCV7	4	?
2014	68	19F	PCV7	4	CSF leakage history of meningitis

5.11.7 *Literature*

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5.12 Human papillomavirus (HPV) infection

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5.12.1 *Key points*

- Incidences of HPV-associated cancers and deaths related to HPV-associated cancers have slightly increased in the last decade in the Netherlands.
- The vaccine-effectiveness of the bivalent vaccine against incidental and persistent infections in a prospective cohort study conducted at

approximately three years post-vaccination was estimated at 73% and 100%, respectively, for HPV16/18.
- The prevalence rates of HPV amongst visitors of an STI clinic are high, with the highest prevalence among women.
- The Netherlands changed the schedule for HPV-vaccination from a three-dose schedule (0, 1, 6 months) to a two-dose schedule (0, 6 months) for girls born in 2001 and after.

5.12.2 Epidemiology

A persistent human papilloma virus (HPV) infection of a high-risk type is necessary to cause the development of cervical cancer. It can also cause vaginal, vulvar, penile, anal, mouth/oral and oropharyngeal cancer. High-risk HPV infections are estimated to cause 88% of anal cancers, 70% of vaginal cancers, 43% of vulvar cancers, 50% of penile cancers and 39% of oropharyngeal cancers, including the tonsils and base of tongue [1]. Figure 5.12.1 and Figure 5.12.2 present the incidences of HPV-associated cancers and deaths related to HPV-associated cancers. Data for 2013 are not available yet.

Genital warts are caused by low-risk HPV types 6 and 11. In 2013, the number genital warts diagnoses at sexually transmitted infections (STI) clinics was 2,057. The positivity rate decreased from 2.9% in 2009 to 1.5% in 2013. The number of diagnoses of genital warts by general practitioners (GPs) was estimated at 38,483 in 2012, which as comparable to the numbers of 2010 and 2011 [2].

5.12.2.1 Change of vaccination schedule

In December 2013, the European Medicines Agency (EMA) approved a two-dose schedule (0, 6 months) for the bivalent vaccine for girls up to 15 years of age [3]. From 2014 onwards, all Dutch girls up to 14 years of age will receive HPV-vaccination in a two-dose vaccination schedule. Reactogenicity and immunogenicity of the two-dose schedule in the Netherlands will be monitored closely by the National Institute for Public Health and the Environment (RIVM).

5.12.3 Research

5.12.3.1 HPV amongst vaccinated and unvaccinated adolescents (HAVANA)

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. For this reason, vaginal self-swabs and questionnaires are collected in this cohort and these are tested for the presence of HPV DNA. Vaccine-effectiveness (VE) against incident and persistent HPV infections was estimated using data from the first three years. VE (including 95%CI) against incident HPV16/18 infections was 73% (47%-86%) and against HPV16/18/31/45 it was 72% (51%-84%). Against persistent infections, VE was 100% and 79% (-89%-98%), respectively. A low VE was found in girls who were already positive at baseline, i.e. before vaccination [4].

5.12.3.2 HPV prevalence among young STI clinic attendees (PASSYON study)

To monitor possible changes in the HPV dynamics over time in the post-vaccination era compared with the pre-vaccination era, a biennial cross-sectional study among 16 to 24 year-old male and female STI clinic attendees was set up [5]. In 2009, 2011 and 2013, the first three rounds of this study took place in a selection of STI clinics located throughout the Netherlands. The anogenital samples collected were analysed for the presence of HPV DNA and the specific HPV type was determined. Preliminary results show a statistically significant decrease in HPV-16 prevalence in 16 to 20 year-old women, from 15% in 2009 and 2011 to 8% in 2013. A non-significant decrease in HPV-16 was observed in men aged 16 to 20 years, and in men and women aged 21 to 24 years. Patterns in HPV-18 were less clear cut. A potential confounding of trends by other STIs and behavioural changes over time still needs to be explored. This study is ongoing [6].

5.12.3.3 Characteristics of vaccinated and unvaccinated girls

A randomly-selected nationwide sample of 16-17 year-old girls, who were eligible for the catch-up campaign in 2009, were invited to participate in a questionnaire study. A knowledge scale score and multivariable analyses identified variables associated with vaccination status. Vaccinated and unvaccinated participants were comparable with regard to education, ethnicity, most sexual risk behaviour (steady partner, condom use, ever had an STI, mean age of sexual debut, sex of partner and number of causal partners) and had similar knowledge scores on HPV transmission and vaccination. However, unvaccinated girls lived in more urbanised areas, were more likely to have a religious background, were less likely to ever had sex and to use contraceptives, although they had a higher mean of lifetime sexual partners than vaccinated girls. Thus, unvaccinated girls seem not to have a disproportionately higher risk of being exposed to HPV than vaccinated girls. Irrespective of vaccination status, 81% of the girls were aware of the causal relationship between HPV and cervical cancer, but the awareness of the necessity of cervical screening despite being vaccinated was limited [7].

5.12.3.4 Type specific clustering

Patterns of type-specific clustering were studied using vaginal self-samples of three cross-sectional studies in the Netherlands; 25 different HPV genotypes were compared. The prevalence of any HPV type was 14% in a population-based study (Nijmegen), 54% in the chlamydia screening intervention (CSI), and 73% in a study among attendees of STI clinics (PASSYON study). Overall, multiple HPV infections were detected in 26% of the women. Types differed significantly in their tendencies to be involved in co-infections, but no evidence for particular type-type interactions was found. Associations between HPV-genotypes differed by study population. The population with the lowest-risk for infection showed the strongest associations between types and vice versa. No indications of specific pairwise interactions were found, although it was suggested that clustering differs among HPV types and varies across risk groups [8].

5.12.3.5 Serological surveys for monitoring the indirect effects of HPV vaccination

Serological surveys offer the possibility to monitor the indirect effects of vaccination by comparing successive age-specific seroprevalence figures in the non-vaccinated population. To evaluate how HPV vaccination will affect type-specific seroprevalence profiles over time, we developed a model that projects the effects of bivalent HPV vaccination on levels of naturally occurring antibodies against HPV-16. Over the first decade of the vaccination programme, we expect a reduction in HPV-16 seroprevalence of 55% and 70% among 16 to 26 year-old non-vaccinated women and men, respectively, if the current 60% vaccine uptake among preadolescent girls is continued. These reductions become more pronounced over time, especially if vaccine uptake increases.

5.12.3.6 Modelling HPV transmission in men who have sex with men

Men who have sex with men (MSM) are at increased risk for HPV-related malignancies, especially for anal cancer, which is caused almost exclusively by HPV-16. As MSM are not expected to benefit from the vaccination of preadolescent girls, specific prevention efforts for MSM are warranted. To address the feasibility of targeted HPV-16 vaccination, we are currently developing a transmission model for HPV-16 transmission in MSM. The model is calibrated to age-specific anal and penile HPV-16 infections among participants of the HIV and HPV in the MSM (H2M) study. This study provides a 24-month follow-up of type-specific HPV prevalence, acquisition and clearance in approximately 800 high-risk MSM, of whom 40% are HIV-infected. The model will provide insight into the cumulative risk of anal HPV-16 infection by age and the risk of re-infection after prior exposure to HPV-16, stratified by HIV status. If possible, we also intend to estimate the efficiency of penile-to-anal versus anal-to-penile HPV-16 transmissibility. These estimates can inform future analyses on the cost-effectiveness of targeted vaccination of MSM.

5.12.3.7 HPV-specific antibody responses induced by infection in high-risk groups

The HIV & HPV in MSM (H2M) study is a prospective cohort study, in which nearly 800 HIV-negative and HIV-infected men who have sex with men (MSM) aged 18 years or older were tested semi-annually for anal, penile and oral HPV DNA and HPV serology during 24 months of follow-up per participant (Amsterdam, 2010-2013).
Type-specific HPV seroconversion against =1 of the 7 HPV types was observed in 19% of HIV-negative and 23% of HIV-infected MSM at risk within one year. Incident or persistent anal HPV infection was an independent determinant for seroconversion in HIV-negative MSM, suggesting that seroresponse varies per anatomical site, and that persistent HPV infections are more likely to elicit a detectable humoral immune response [9]. In addition, high antibody concentrations showed no protective effect against subsequent type-specific anal or penile HPV infection within one year, indicating that in a population of sexually active adult MSM, naturally induced HPV antibodies may not protect against subsequent HPV infection [9, 10].

5.12.3.8 Viral load

HPV viral load is relevant in HPV infections; it reflects the productivity of DNA replication of an HPV infection at a given time point. Viral load levels are suggested to play a role in defining the course of the infection. Several studies have found that high viral loads can be indicative of infection persistence, which in turn could lead to cervical malignancies. In order to establish and monitor HPV type-specific prevalence and incidence, before and after HPV vaccination, a variety of studies were set up (as was mentioned above). Evaluating the effects of HPV-16 and HPV-18 vaccination on viral load could lead to further insights into infection progression and possibly the prevention of persistence. Currently, HPV-16 and HPV-18 viral load assays have been set up. This has resulted in a highly sensitive and specific L1-targeting real time PCR assay for the quantification of HPV-16 and HPV-18. The assay was validated using HPV-16 and HPV-18 DNA cloned in plasmids. Viral load values were determined in vaginal self-swabs from the CSI. We compared the viral load of transient and persistent HPV-16/HPV-18 infections. HPV-16 persistent infections have significantly higher initial viral loads than transient infections, with persistency being defined as HPV-16 positive tests in two subsequent samples. The same was found for HPV-

18 persistent infections when compared to transient infections. This study is still ongoing.

5.12.3.9 HPV with or without chlamydia

Chlamydia could increase susceptibility to HPV infection [11] or decrease the efficient clearance of an existing HPV infection, thereby increasing the chance of developing cancer [12-14].
In a large follow-up study of young and sexually active women [15], we assessed the possible association between chlamydia infection and the subsequent acquisition and persistence of infection with carcinogenic HPV types (data not yet published). We found that HPV incidence rates were significantly higher among women with chlamydia co-infection as compared with those without. This could reflect enhancement in HPV acquisition by chlamydia or residual confounding through unobserved risk factors. No significant association was found for chlamydia and HPV persistence. Yet the results do give reason to explore more fully the association between chlamydia and HPV type-specific persistence.

5.12.4 International developments

In December 2013, the EMA approved a two-dose schedule (0, 6 months) for the bivalent vaccine for girls up to 15 years of age. In February 2014, the EMA also approved a two-dose schedule for the quadrivalent vaccine. Currently, the two-dose schedule has been adopted in Quebec, Switzerland, the Netherlands and Mexico [16]. The European Committee granted the use of the quadrivalent vaccine for primary prevention of anal cancer and precancerous anal lesions among 9-26 year-olds.
In Sweden, a significant difference in incidence rates between the three-dose and two-dose schedule (girls 10-16 years) was reported, with incidence rates of 101 (95% CI 80-122) and 160 (95% CI 107-214), resulting in an incidence rate difference of 59 per 100,000 person-years (95% CI 2-117) [17]. The incidence rates were determined irrespective of the interval between different doses and girls could be vaccinated with the bivalent or quadrivalent vaccine.

Postmarketing surveillance in Australia showed that a decrease in vaccine-targeted HPV genotypes in vaccinated women was detected 6 years after introduction of the quadrivalent vaccine. Lower prevalence of vaccine-targeted types was also found in unvaccinated women, indicating herd immunity [18]. Australia was the first country to introduce HPV vaccination in 2007. Girls and women aged 12-26 years were targeted for vaccination. In the first four years after introduction of vaccination, overall VE among women 18-24 years of age against high grade cervical abnormalities was estimated at 46% and against any other cytological or histological abnormalities at 34%. While vaccine effects were significant for 15-18 year-olds (VE 57%) and 19-22 year-olds (VE 53%), in older women there was little evidence of vaccine effects [19]. The overall VE of two doses, independent of the moment of the second dose, was 21%.
In Denmark HPV vaccination was introduced in 2009 among twelve-year-old girls, supplemented in 2008 with a catch-up programme among 13 to 15 year-old girls. In 2012, a second catch-up programme for women up to 27 years old was started. The incidence of any abnormal cytological outcome in Denmark among women younger than 18 years and in women between 18 and 20 years of age significantly decreased (estimated annual percentage change of -33.4% (95% CI -49.6 - -12%) and -12.6% (95% CI -19.3 - -5.3%), respectively) after the introduction of the quadrivalent vaccine. Among these age groups vaccination coverage was highest [20].

Blakely et al. estimated the cost-effectiveness of the implemented HPV vaccination programme in New Zealand, dispersed across schools and primary care (at a vaccination coverage of 47%), and two alternatives: school-based only (assumed coverage 73%) and mandatory school-based vaccination but with opt-out permitted (coverage 93%) [21]. The current HPV vaccination programme proved to be the most cost-effective strategy. Mandatory vaccination appeared least cost-effective.
Two studies were conducted to evaluate the quadrivalent HPV vaccination including boys. Burger et al. calculated the health outcomes and costs of the different HPV-related diseases in Norway [22]. He found that expanding the HPV vaccination programme to boys may be cost-effective. However, increasing the coverage in girls would be the most effective and cost-effective option. Bresse et al. found more favourable results, vaccinating both boys and girls in Austria would result in an ICER of €10,033/QALY [23].
Randomized clinical trials are currently examining the efficacy of a nonavalent HPV vaccine. Drolet et al. compared the potential cost-effectiveness of the nonavalent and quadrivalent HPV vaccines in Canada [24]. Under base-case assumptions and at equal price, the nonavalent vaccine is more cost-effective than the quadrivalent vaccine, even when assuming both a shorter duration of protection and lower vaccine-type efficacy.

5.12.5 *Tables and figures*

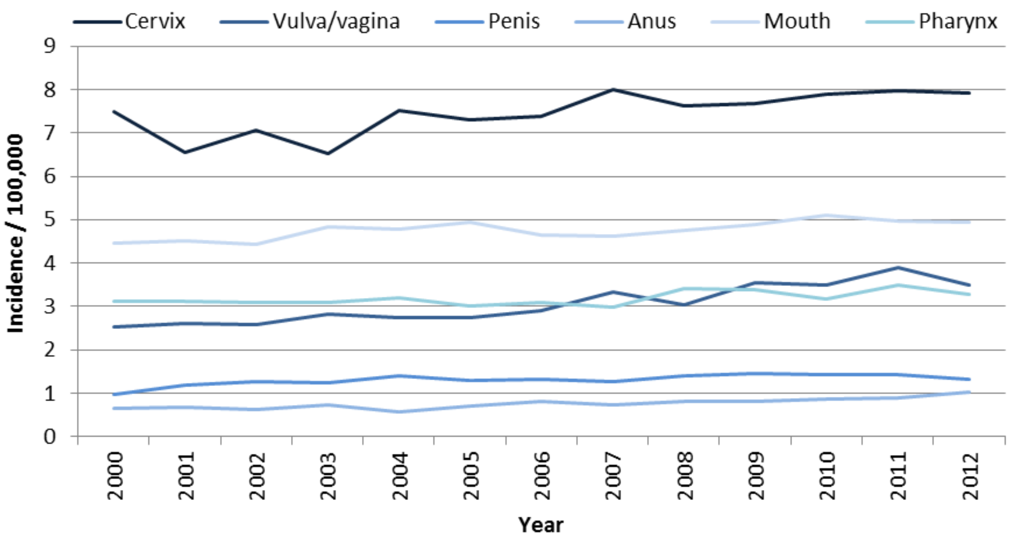

Figure 5.12.1 Incidence / 100,000 (standardised by the European standardized rate) of new cervical, anogenital, mouth/oral and pharynx/pharyngeal cancer cases in the Netherlands 2000-2012, by cancer type (the Netherlands Cancer Registry (NKR))

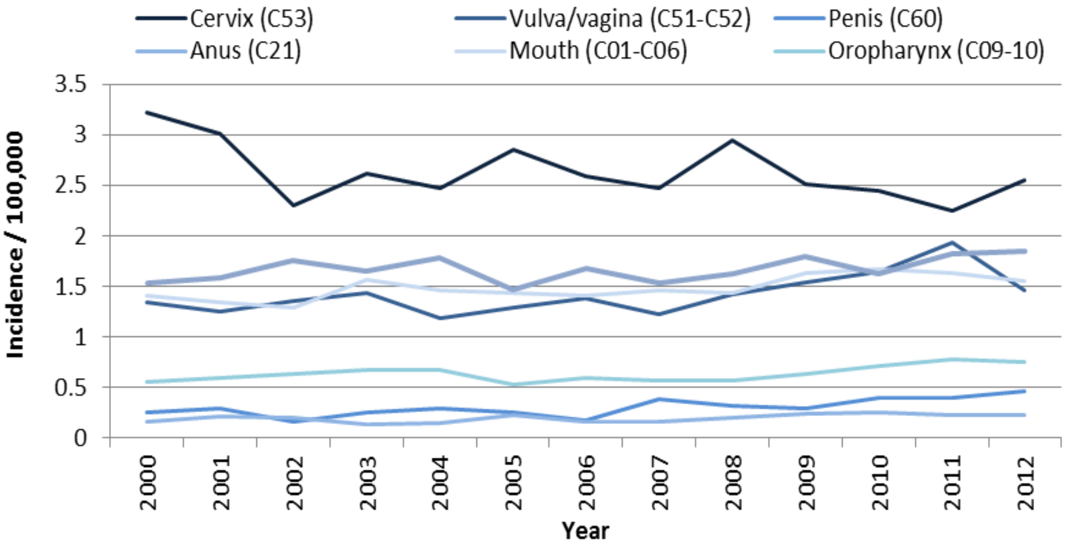

Figure 5.12.2 Incidence / 100,000 of deaths related to cervical, anogenital, mouth, oropharynx and pharynx cancer cases in the Netherlands 2000-2012 by cancer type (Statistics Netherlands (CBS))

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

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6 Future NIP candidates

6.1 Rotavirus infection

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6.1.1 *Key points*

- Incidence of rotavirus associated gastroenteritis in the Netherlands in 2013 was slightly higher than in 2012.
- In 2013, G1[P8] was most commonly found in the Netherlands, followed by G3P[8], G2P[4] and G4P[8].

6.1.2 *Epidemiology*

The Working Group Clinical Virology reports the number of rotavirus positive results weekly (see Appendix 2). In 2013, 1,487 diagnoses of rotavirus were reported, which is slightly higher than in 2012 (1,287 isolates) but lower than in 2011 (1,504 isolates). The reports have a clear seasonal pattern, with the peak in March, except for 2013 when the peak was in April (Figure 6.1.1). Estimated hospitalisations in 2013 are not available yet.

6.1.3 *Pathogen*

The Centre for Infectious Disease Research, Diagnostics and Screening (IDS) of the RIVM received 299 faeces samples that tested positive for rotavirus in peripheral laboratories, 280 of these samples could be typed (Table 6.1.1). G1P[8] is most commonly found since 2008. Nevertheless, other genotypes have become more prevalent in 2012 and 2013 (Figure 6.1.2). Co-infections with rotavirustypes were detected in 30 samples in 2013 (11%), showing an increasing trend over the past years (1%, 3%, 6% and 8% from 2009 to 2012).

6.1.4 *Research*

The IDS of the RIVM participates, together with 14 other countries, in EuroRotaNet. This European Rotavirus Network was established in January 2007; IDS joined the project in June 2008. Within this project, Dutch microbiological laboratories can send rotavirus-positive faeces samples to IDS for typing, using reverse line-blot hybridisation (RLB) and/or sequencing. EuroRotaNet combines the results of the participating countries to create 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.

6.1.5 *International developments*

Both the monovalent Rotarix vaccine and the pentavalent Rotateq vaccine are marketed internationally [1, 2]. One other live attenuated rotavirus vaccine has been licensed to date. This vaccine is manufactured in China and is derived from a lamb rotavirus (Lanzhou lamb rotavirus vaccine). Its efficacy, however, is not supported by robust field studies and it is not available outside China. Local development of other live, oral vaccines is ongoing in Indonesia, India, Brazil and Vietnam.

As of June 2014, 64 countries have included rotavirus vaccination in their infant immunisation programmes [3]. In the European Economic Area, 8 countries offer funded rotavirus vaccination to infants as part of a national immunisation programme (Austria, Belgium, UK, Finland, Germany, Norway, Latvia, Luxembourg) [4]. Several other countries are at various stages of issuing national recommendations or integrating rotavirus vaccination into their national immunisation programmes.

Post-implementation studies on the real-world impact of rotavirus vaccination now include data covering up to 6 years post-implementation. In high-income countries, persistent marked reductions are seen consistently in the number of rotavirus-related hospitalisations in infants and young children after implementation of the vaccine. Proportionate reductions vary between 74% and 95%, depending on the age group included in the analysis, with the highest reductions observed in studies including infants younger than 2 years of age only [5-9].

An important and unanticipated benefit of universal infant rotavirus vaccination is the reduction of rotavirus disease in unvaccinated children due to a reduction in transmission rates among a diminished population of susceptible infants. These herd effects have been reported from Australia, the US, Belgium, Austria and Brazil, among other countries. Herd protection is most pronounced in children 2 to 5 years old and in those too young to be vaccinated, but it varies substantially by study and by study year, with a percentage of reduction between 0% and 80% [10-16]. In the US, winter gastroenteritis hospitalizations in older children and adults have also declined since the introduction of infant rotavirus vaccination, groups not previously well-recognized to have substantial rotavirus disease [17, 18]. In addition, marked reductions up to 95% in nosocomial rotavirus infection rates have been observed, indicating reduced transmission within the hospital setting [16, 19].
In the US, with rotavirus vaccine coverage rates of 60 -79%, biennial peaks of rotavirus infections have been observed since introduction of vaccination [6, 7, 20], although the intensity of these epidemics is much lower than it was during the pre-vaccine era. This pattern was previously suggested for high-income countries by modelling projections [21], but has not been confirmed in other countries with higher coverage rates such as Australia, Belgium and Austria. Another interesting observation from two recent studies forms the decline in hospitalisations for childhood seizures after the introduction of rotavirus vaccination. Clinical neurologic illness has been linked to rotavirus infection in numerous studies and case reports, which prompted the hypothesis of a potential vaccination effect on childhood seizure incidence. In Spain, reductions in hospitalisations for childhood seizures between 16% and 42% have been observed since introduction of rotavirus vaccination, with higher reductions seen in the years with higher rotavirus vaccine coverage rates [22]. In the US, data from the Vaccine Safety Database were used to compare the incidence of being hospitalised or visiting the emergency department for seizures in cohorts of vaccinated and unvaccinated children. A statistically significant protective association was observed between a full course of rotavirus vaccination vs. no vaccination for both first-ever seizures (risk ratio = 0.82; 95% CI, 0.73–0.91) and all seizures (risk ratio = 0.79; 95% CI, 0.71–0.88) [12].

Recently, a German and a Spanish economic evaluation have been performed to support informed decision-making on possible implementation of rotavirus vaccination into the national immunisation programme [23, 24]. Both studies used a deterministic Markov model to estimate the cost-effectiveness. Applying a societal perspective, a vaccination strategy with Rotarix® in the German situation would cost €64,985 per QALY gained, whereas the implementation of

RotaTeq® would cost €93,355 per QALY gained. The introduction of the vaccination using RotaTeq® as a universal infant vaccination in the Spanish setting would lead to an ICER of €210,167 per QALY gained. Both studies concluded that, given the current vaccine prices, introduction of a universal infant rotavirus vaccination would not be cost-effective. Nevertheless, Germany included rotavirus vaccination in their national immunisation programme in 2013 [25].

6.1.6 Tables and figures

Table 6.1.1 Number of reported laboratory diagnoses of rotavirus, and number of positive samples sent to and typed at the RIVM, 2009-2013

Year	Laboratory diagnoses	Samples at RIVM		Samples typed at RIVM	
		N	% of diagnoses	N	% of samples at RIVM
2009	1,935	869	44.9%	830	95.5%
2010	2,180	578	26.5%	547	94.6%
2011	1,504	414	27.5%	400	96.6%
2012	1,287	276	21.4%	265	96.0%
2013	1,487	299	20.1%	280	93.6%

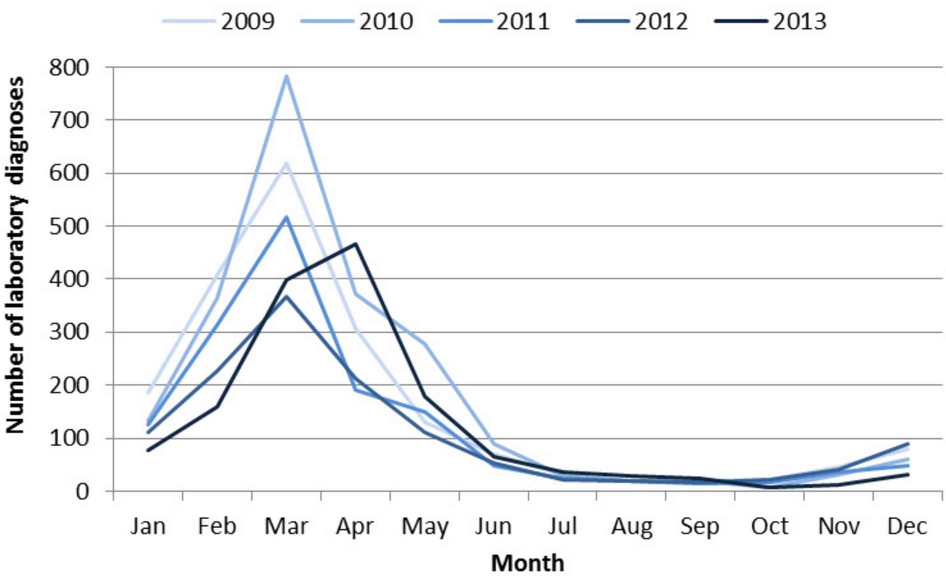

Figure 6.1.1 Reported laboratory diagnoses of rotavirus per month, 2009-2013

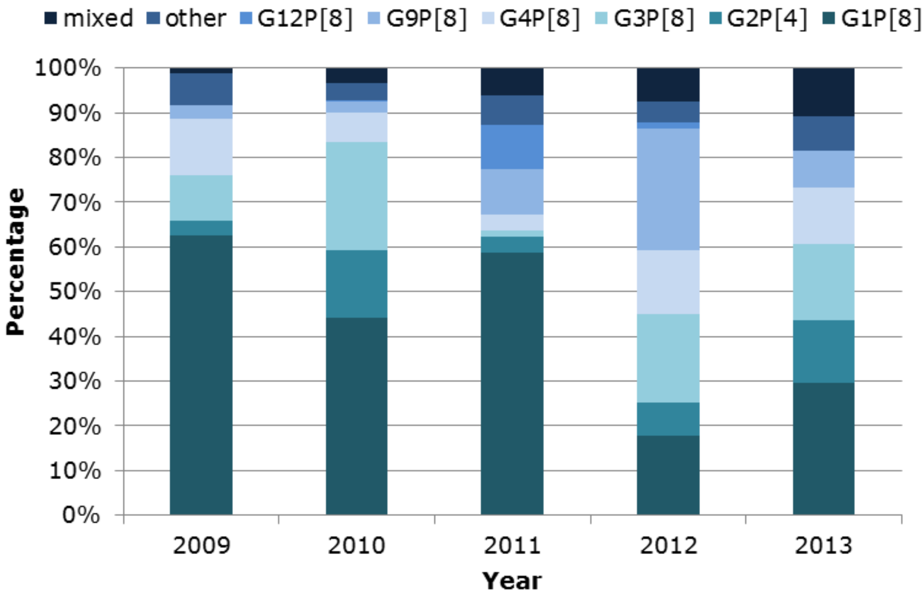

Figure 6.1.2 Rotavirustypes as detected at the RIVM, 2009-2013

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6.2 Varicella zoster virus (VZV) infection

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6.2.1 Key points

- It is difficult to determine whether changes occurred in the VZV epidemiology in 2013. The methodology for calculating the incidence of varicella and herpes zoster in general practice has been changed from 2012 onwards and these data, as well as the hospital and mortality data, are not yet available for the year 2013.
- The willingness to vaccinate against varicella was found to be relatively low in the Netherlands among both professionals (21%) and parents (28%). A low to medium uptake of varicella vaccination in the population is undesirable from a public health perspective. This stresses the importance of careful monitoring to anticipate the potential negative impact of a higher mean age of infection.

6.2.2 Epidemiology

Periodic outbreaks of varicella occur, with an inter-epidemic cycle of two to five years [1]. In contrast, the incidence of herpes zoster has been stable over time [2]. According to the new estimation method of NIVEL (see Appendix 1), the incidence of herpes zoster is higher than it was according to the old method (Table 6.2.1a). Table 6.2.1b, based on a selection of 74 practices with good quality registration, also shows that there was more fluctuation in the varicella incidence than in herpes zoster incidence in the period 2010-2012. The incidence of varicella episodes per 100,000 population is highest in the age groups below five years, whereas the incidence of herpes zoster episodes is highest in the age groups above 50 years (Figure 6.2.1). The incidence of hospitalisations due to varicella is highest among new-borns, while the incidence of hospitalisations due to herpes zoster is highest among the oldest age groups (Figure 6.2.2).
National death certificate data tend to overestimate the number of deaths in which herpes zoster is the underlying or contributing cause of death [3]. If we apply Mahmud's rate of deaths, in which herpes zoster was validated as the underlying cause of death (0.25 (range 0.10–0.38) per 1 million population) on the Dutch population in 2012, we would expect 4.2 deaths (range 1.7–6.4) instead of the 21 deaths that were reported in 2012 (Table 6.2.3).

6.2.3 Pathogen

Ihira et al. showed that cycling probe real-time PCR can differentiate between the VZV wild-type strain and the vOka strain in clinical samples [4]. Rapid differentiation is important for monitoring adverse events of varicella vaccination, and for distinguishing between wild-type VZV and the vaccine strain among both varicella and herpes zoster cases.

Using molecular research, the impact of universal varicella and/or zoster vaccination on the distribution of wild-type VZV, the emergence of wild-type/vaccine recombinants and the ability of the vaccine type to cause varicella (in unvaccinated people) and herpes zoster (among vaccinated people) can be studied.

6.2.4 *Research*

According to the Health Council of the Netherlands, some vaccines available are rarely used in the Netherlands, mainly due to the way in which vaccination care is currently organized [5], see Chapter 3. Potential health gains, therefore, are being left untapped. One of the examples of underused vaccines mentioned is the varicella vaccine. With regard to varicella, it might be expected that vaccination within as well as outside the NIP would result in low national coverage. The willingness to vaccinate against varicella was found to be relatively low in the Netherlands among both professionals (21% pro universal childhood vaccination) and parents (28% positive intention to vaccinate own child if included in NIP) [6]. Furthermore, an earlier study confirmed the relatively low varicella disease burden compared with other countries [7]. With regard to varicella vaccination, one must be aware that a low to medium vaccination coverage poses potential risks. These risks are the formation of an unvaccinated population at risk of delayed and thus more severe disease and the potential rise in herpes zoster incidence due to diminishing exogenous boosting [8]. This stresses the importance of monitoring the epidemiology of varicella, also when vaccination is not included in the NIP but available for individuals through, for example, collective insurance. From a public health perspective, it is undesirable to have a low to medium uptake of varicella vaccination in the population. This stresses the importance of careful monitoring to anticipate the potential negative impact of a higher mean age of infection. A cost-effectiveness analysis of varicella vaccination in the Netherlands is ongoing.

6.2.5 *International developments*

ECDC developed a preliminary guidance on varicella vaccination in the European Union to support EU Member States in their national decision-making process with regard to varicella vaccination [9]. The main conclusions drawn are that universal childhood varicella vaccination has shown to be highly effective in reducing the burden of varicella disease, but there is limited knowledge about the

- duration of vaccine-induced immunity;
- optimal time for a second dose;
- potential need for further booster doses later in life;
- impact of vaccine coverage on the long-term epidemiology of the disease;
- severity of breakthrough varicella with an increase in time since vaccination;
- risk of increasing complications due to varicella following shifts in the mean age of infection after vaccine introduction;
- risk of complication in adult breakthrough varicella cases that occur several decades after vaccination; and
- the potential increase in HZ incidence.

ECDC recommends that countries, while waiting for more evidence on several aspects of varicella vaccination as described above, should assess the national epidemiological and socioeconomic situation, as well as the possibility of achieving high vaccination coverage.

In Germany, the vaccine effectiveness against varicella was estimated at 86.4% (95% CI 77.3%-91.8%) for any severity and 97.7% (95% CI 90.5%-99.4%) for moderate or severe disease [10]. A long-term study of Baxter et al. showed that the average incidence of varicella in a cohort vaccinated in the first year of universal vaccination (63% with one dose and 37% with two doses) was 15.9

per 1,000 person-years [11]. Vaccine effectiveness after 14 years follow-up was 90% and there was no indication of waning over time. Most varicella cases were mild (<50 lesions) and occurred early after vaccination. No varicella cases were reported after a second dose. Bialek et al. saw that, from 2006 (start recommendation second dose) to 2010, varicella incidence declined by 76.3% in West Philadelphia, PA and by 67.1% in Antelope Valley, CA [12]. However, the median age among both vaccinated and unvaccinated patients increased, and there were some breakthrough cases among 2-dose vaccinees (mostly mild cases). A study in Beijing also showed a significant increase in the number and proportion of adult varicella cases (=20 years of age) in a population with high 1-dose coverage in young children with declining disease incidence [13]. A significant decrease in the incidence of reported varicella cases in the period 2006-2010 was seen in New Hampshire as well [14]. Daly et al. also hypothesized that the decrease in the proportion of mild varicella and increase in the proportion moderate varicella might be attributable to the change in the relative age distribution of cases (i.e. at higher age one is more likely to experience moderate or severe disease).
According to a review of Bonanni et al., literature to date indicates a relatively high rate of primary vaccine failure (including those who did not mount an adequate response for protection, despite an initial antibody response) and limited evidence of secondary vaccine failure among 1-dose vaccinees. This suggests that a short interval between 2 doses might be favourable for countries considering the introduction of universal varicella vaccination [15]. This was also suggested by Prymula et al., who investigated the protection against varicella with two doses of MMRV vaccine (95% effectiveness against all varicella and >99% against moderate to severe varicella) versus one dose of monovalent varicella vaccine (65% effectiveness against all varicella and 91% against moderate to severe varicella) [16].

An adjuvanted VZV glycoprotein E (gE) subunit vaccine against herpes zoster is under development. In a phase II study, Chlibek et al. showed that AS01 adjuvant improved the immunogenicity of gE, while safety and reactogenicity profiles remained acceptable [17]. The Singles Prevention Study (SPS) showed that postvaccination GMT was correlated with protection against herpes zoster, although a protective threshold could not be determined [18]. The vaccine effectiveness in a general population-based setting (a cohort study of 766,330 individuals) was estimated at 48% (95% CI 39%-56%) against herpes zoster and 59% (95% CI 21%-79%) against post-herpetic neuralgia [19]. Hales et al. found that age and sex-standardised herpes zoster incidence increased by 39% from 10.0 per 1,000 person-years in 1992 to 13.9 per 1,000 person-years in 2010 [20]. They concluded that there was no evidence to suggest that this increase has been influenced by the varicella vaccination programme. Firstly, the rise in incidence started before 1996 and did not accelerate after the implementation of a varicella vaccination programme with high coverage. Secondly, the same pattern was seen in several states despite differences in vaccination coverage. Finally, the mean age of herpes zoster cases did not decrease during this period, which might be expected if external boosting plays a role in maintaining protection. However, according to others, several issues remain to be addressed before confirming that widespread varicella vaccination has no influence on herpes zoster incidence in unvaccinated people [21]. A study of Weinmann et al. showed that the incidence of herpes zoster in vaccinated children was 79% lower than it was in unvaccinated children. Wild-type virus caused half of the herpes zoster cases among vaccinated children [22].

Since 2004, routine childhood varicella vaccination has been implemented in Germany. Recently, Ultsch et al. have performed an economic evaluation of zoster vaccination for the elderly, using a static Markov-cohort model, which compared a vaccine-scenario with no vaccination [23]. The base-case-analysis yielded an ICER of €28,146 per QALY gained. Vaccination at the age of 60 was identified in most (sensitivity) analyses to be the most cost-effective vaccination strategy. In sensitivity analyses, vaccine price and vaccine effectiveness proved to be the most critical input parameters. A price per vaccine dose below €26.50 (i.e. >80% below the price in the base case analysis) would result in potential cost-savings.

6.2.6 *Tables and figures*

Table 6.2.1a Estimated incidence per 100,000 of episodes of varicella (ICPC-code A72) and herpes zoster (ICPC-code S70), based on NIVEL-PCD, using the old method (2004-2011) and the new method (2012) (rounded off to tens)

Syndrome	2004	2005	2006	2007	2008	2009	2010	2011	2012
Varicella*	250	190	300	210	(160)	(110)	(180)	-	-
Varicella**	200	130	260	230	290	180	210	230	-
Varicella***									250
Herpes zoster**	310	350	370	310	340	360	360	360	-
Herpes zoster***									550

* Dutch Sentinel General Practice Network (CMR) [24]; starting in 2008, this network has changed from registration on paper to electronic reporting, which may have resulted in underreporting of the weekly number of varicella patients. Therefore, we used data from NIVEL-PCD from 2008 onwards.
** NIVEL-PCD, old method [25].
*** NIVEL-PCD, new method [26].

Table 6.2.1b Estimated incidence per 100,000 episodes of varicella (ICPC-code A72) and herpes zoster (ICPC-code S70), based on a selection of NIVEL-PCD using the new method (2010-2012) (rounded off to tens)

Syndrome	2010	2011	2012
Varicella*	390	340	270
Herpes zoster*	610	650	680

* NIVEL-PCD, new method: based on 74 practices with good quality registration [27].

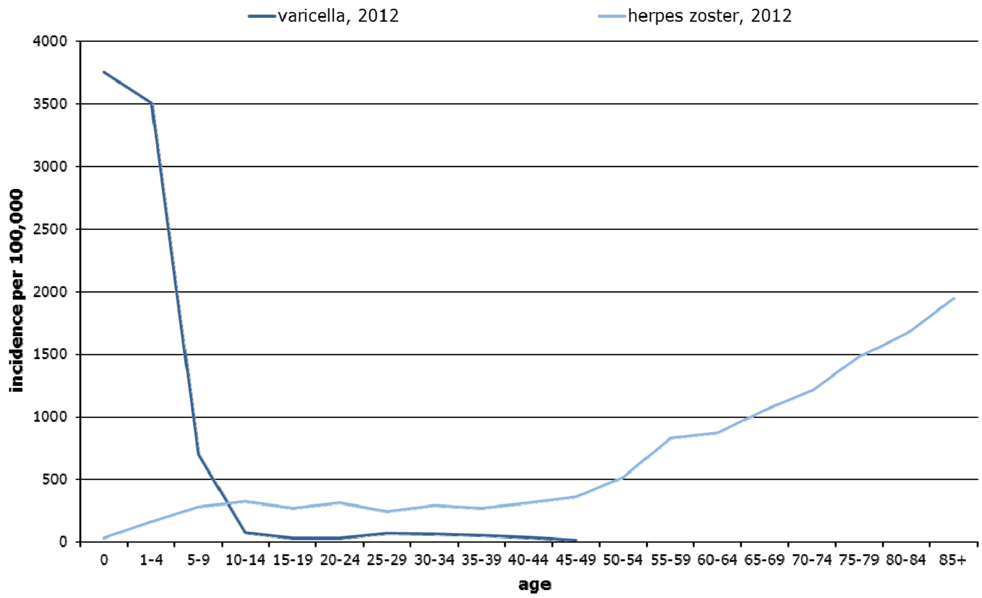

Figure 6.2.1 Estimated incidence per 100,000 episodes of varicella (ICPC-code A72) and herpes zoster (ICPC-code S70) in 2012 by age group [26]
Note: Varicella cases in people older than 49 are only sporadically reported by GPs and are therefore not included.

Table 6.2.2 Incidence per 100,000 of hospitalisations due to main and side diagnosis varicella (ICD-10 code B01) or herpes zoster (ICD-10 code B02), 2004–2012 [28]

Syndrome	**'04**	**'05**	**'06**	**'07**	**'08**	**'09**	**'10**	**'11**	**'12**
Varicella – main	1.7	1.5	1.9	1.4	1.7	1.5	1.9	1.7	1.5
Varicella – main + side	2.6	2.2	2.8	2.1	2.4	2.2	2.7	2.6	2.3
Herpes zoster – main	2.5	2.2	1.9	2.0	2.0	2.4	2.1	2.2	2.1
Herpes zoster – main + side	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 Appendix 1).

Note: Admissions for one day have been excluded.

Note: 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.

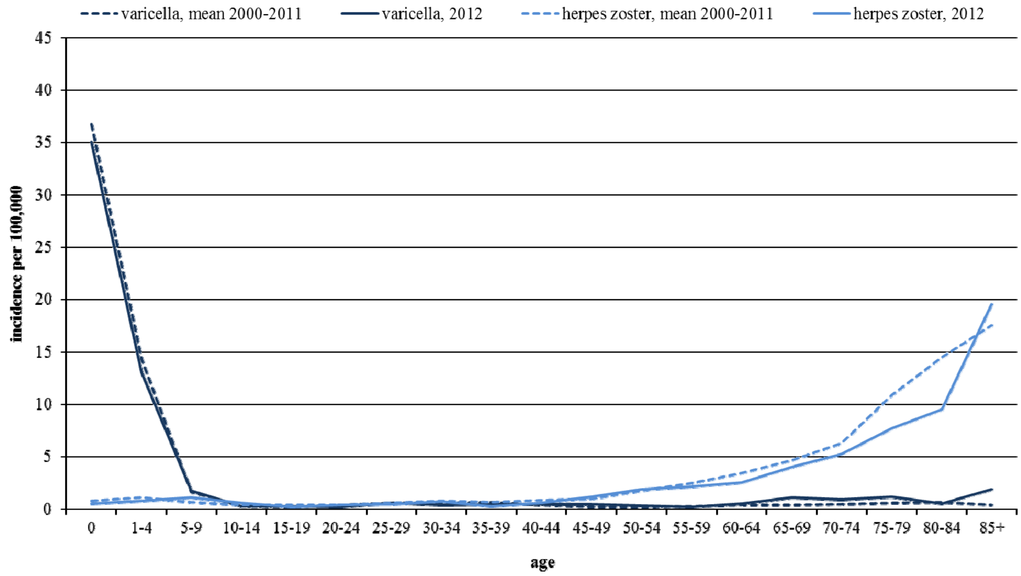

Figure 6.2.2 Incidence per 100,000 of hospitalisations due to main diagnosis of varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02) in 2012 versus mean incidence in 2010-2011 by age group [28]

Table 6.2.3 Absolute number of deaths with main cause being varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02), 2004–2012 [29]

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

6.2.7 *Literature*

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6.3 Hepatitis A

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6.3.1 Key points

- In 2013, the number of hepatitis A infections (110 cases) remained low, as in recent years.
- Fifty-five percent of the Dutch cases were reported to be travel-related, mostly in Morocco and Egypt.

6.3.2 Epidemiology

In 2013, 110 cases of hepatitis A were reported in the Netherlands, corresponding to 0.6 cases per 100,000 inhabitants. This is a small decrease compared with 2011 (125 cases) and 2012 (121 cases), and the lowest since hepatitis A became notifiable in 1999 (Figure 6.3.1 / Appendix 2). More than a quarter of the reported patients (27%) were hospitalised, a bit higher proportion than in previous years 2003-2009 (8-23%). The mean age of patients hospitalized with a hepatitis A infection was 38 years (range 6-80 years, 13% aged <19 years) compared with 24 years of age (range 1-81 years, 44% aged <19 years) in non-hospitalised patients. The age distribution over the years 2005-2013 is given in Figure 6.3.2. No mortality due to hepatitis A was reported.

The percentage of travel-related cases was 55% in 2013 (Figure 6.3.1). Morocco (16/61; 26%) and Egypt (12/61; 20%) were reported most frequently; other countries were reported a maximum of three times. Sixteen epidemiologically linked clusters with in total 34 of the 110 cases could be deduced from the reports: 11 clusters were at least partly travel-related, mostly from Morocco (6 clusters); in five clusters no relation with travel was found. The largest cluster contained five reported cases in a family and friend setting. Consumption of food or water was reported as the source of the infection in 15% of the cases, two-thirds of which consumed abroad.

6.3.3 *Pathogen*

IgM-positive samples can be sent to 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 taking a serum sample is not preferred. This is often preferred for young children who are not ill but are possibly related to a cluster. In 2013, a total of 150 serum and faecal samples were tested, 80 (53%) samples of which were positive and 73 (91%) of which could be typed, resulting in 38 unique sequences, with 12 clusters of 2 to 14 cases. There were no large differences seen in the genotype prevalences compared to 2012.

6.3.4 *Research*

Initially, the typing of IgM-positive samples by IDS was done for a period of two years, but is now being continued for an indefinite period of time, as it adds valuable data for the detection and follow-up of clusters and outbreaks. The results are linked to the notifications, where possible, to combine the available information about microbiology and epidemiology. In cases involving a molecular cluster of cases with an unknown source within the Netherlands, or an international molecular cluster of cases, a source-tracing investigation is usually initiated. In 2013, several remarkable molecular clusters were identified, requiring further investigation by the Municipal Health Services (MHS), the Food Safety Authority and RIVM. Three clusters were also investigated together with (inter)national partners and traced back to a suspected common food-related source. In an international cluster of travellers returning from Egypt, strawberries were considered the most likely source. A remarkable finding in this cluster was the fact that vaccination had not been recommended to five of the six cases, including Dutch cases, who sought travel medical advice before travelling (Sane et al. submitted). A second international cluster is still under investigation by EFSA, ECDC and national public health institutions of all countries involved. For this cluster, preliminary findings point to frozen berries as the most likely source of infection [1]. A third cluster only involved Dutch cases visiting a restaurant. This cluster was traced back to fresh mint as the most likely source of infection.

6.3.5 *International developments*

In Alaska, a cohort of 144 persons was followed after vaccination with a three-dose of HAVRIX [2]. After 17 years of follow-up, 58 participants remained (aged 20-24 years), 54 (93%) of which had protective anti-HAV levels. Vaccination schedules 0, 1 and 6 months (100%), and 0, 1 and 12 months (94%) showed better results than vaccination schedule 0, 1 and 2 months (87%). The anti-HAV geometric mean concentrations (GMCs) showed a linear decrease through 10 years after vaccination, but were stable in the following 7 years. A comparison of this three-dose vaccination schedule to a two-dose vaccination schedule (HAVRIX or VAQTA) in the same population and also in childhood showed similar protection at 14 years after vaccination [3].

A review of the protection achieved by a single-dose inactivated HAV vaccination was performed using information from nine published studies in adults and six in children [4]. The results suggested that protection after a single dose could persist for almost 11 years and it appeared that there is no need for a booster dose in the first six years after initial vaccination. When administering a booster vaccination, within 11 years after primary vaccination, protection levels increase or reappear. An original article about the effects of single-dose vaccination in

Argentina was also published [5]. In 2005, a single-dose of inactivated hepatitis A vaccine (HAVRIX, VAQTA, AVAXIM, Virohep-A Junior) was added to the regular immunisation schedule for all children aged 12 months. The mean vaccination coverage for 2006-2011 was 96.8%. The overall incidence dropped by 88% from 66.5 in the pre-vaccination period to 7.9 per 100,000 in the post-vaccination period.

The WHO state in their position paper on HAV vaccines that both inactivated and live-attenuated hepatitis A vaccines are highly immunogenic [6]. In (very) low endemic countries, targeted vaccination of high-risk groups should be considered to provide individual health benefits. High-risk groups include travellers to areas of intermediate or high endemicity, injection drug users and men who have sex with men, but also persons who need life-long treatment with blood products and patients with chronic liver diseases.

6.3.6 *Tables and figures*

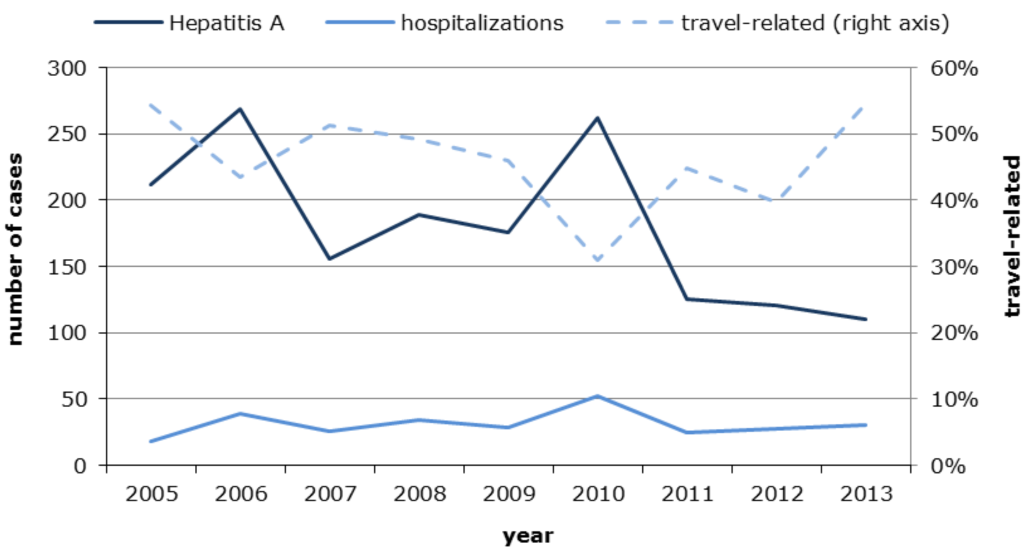

Figure 6.3.1 Number of reported and hospitalised cases of hepatitis A, 2005-2013

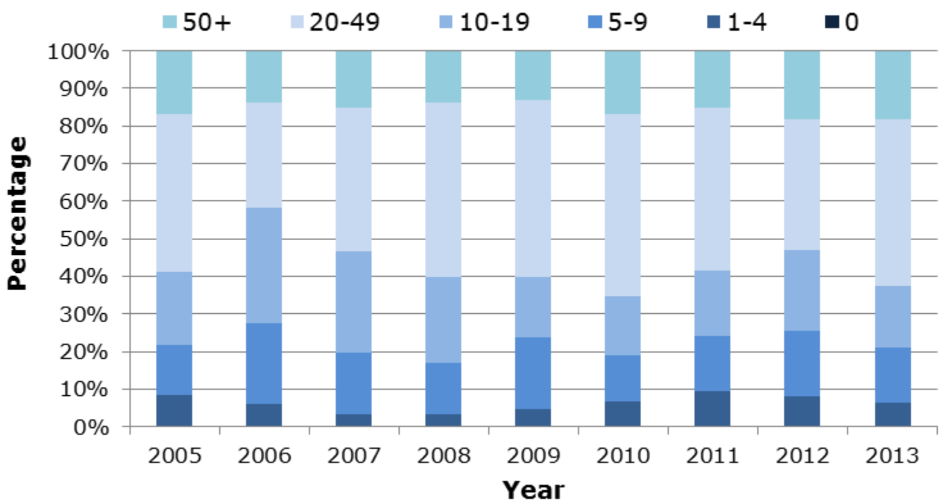

Figure 7.3.2 Age distribution of hepatitis A-cases, 2005-2013

6.3.7 Literature

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6.4 Meningococcal serogroup B disease

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6.4.1 Key points

- In 2013, a small increase in Meningococcal serogroup B (MenB) disease was seen (88 cases in 2013, compared with 76 in 2012), which is due to a small increase among 5-64 year-olds, while among the very young the incidence decreased slightly.
- In March 2014, the UK Joint Committee on Vaccination and Immunisation (JCVI) recommended that the MenB vaccine should be introduced into the UK's routine immunisation schedule for children, provided that it can be obtained at a cost-effective price.

6.4.2 Epidemiology

From 2001 to 2012, the number of patients with meningococcal B disease had been decreasing from 422 to 76, only to slightly increase again to 88 cases in 2013 (Table 6.4.1). The incidence among 0-4 year-olds had decreased from 4.5 to 3.9 per 100,000 in 2012 and 2013, respectively, whereas among those aged between 5 and 64 years the incidence had increased somewhat (0.2 per 100.000 in 2012 to 0.4 per 100.000 in 2013) (Figure 6.4.1). 77% of all meningococcal cases were caused by MenB and in 41% of MenB disease cases it concerned children younger than five years in 2013.

6.4.3 Pathogen

The decline of serogroup B invasive disease was seen among all clonal complexes [1]. Analyses of the sequence variability over a 50-year period of three of the four antigens in the only available MenB vaccine 4CMenB (brand name Bexsero®) showed that isolates expressing fHbp-1.1 and NadA-3.8 circulated for 30 years and NHBA-2 for 50 years [2]. Analyses of the PorA antigen variability over a 60-year period revealed that NonaMen, a MenB vaccine with 18 PorA epitopes developed in the Netherlands (RIVM/Netherlands Vaccine Institute/IntraVacc, Bilthoven), potentially covered 71% of the serogroup B isolates in 1960-1965 and thereafter between 90% and 100% [1].

6.4.4 Research

6.4.4.1 Clinical course of meningococcal serogroups

A national representative surveillance study was conducted on the clinical course and mortality of various meningococcal serogroups in the Netherlands between June 1999 and June 2011. A total of 711 cases of MenB infection were included in this study. 50.1% of the patients presented had meningitis, 16.0% had septic shock and 22.5% had both septic shock and meningitis. Young children were more at risk for a MenB infection and appeared to develop septic shock more often than adults. Overall mortality was 7.7%, with the highest CFR among patients with septic shock (17.3%) and the lowest among patients with meningitis (1.9%) [3].

6.4.4.2 Characterisation of immune responses

A study called 'Imm-f@ct: Characterization of immune mechanisms in measles and other infectious diseases' was started in 2014 at the RIVM, which also includes meningococcal serogroup B samples. This study is intended to explore the immune response, with special focus on the cellular immunity, against MenB. The most important theme for MenB is the impact of CD4 T cell epitope 'PorA region 4' in antibody responses to PorA loop 4.

6.4.4.3 Carrier state of Meningococcal serogroups

A clinical study (CarMen – NTR3785) was performed to investigate the oropharyngeal meningococcal carriage, particularly serogroup B, in adolescents and young adults aged 13-22 years. In addition, the rate of acquisition of serogroup B meningococci in adolescents during transition from high school to tertiary school (MBO/HBO/university) will be assessed.

6.4.4.4 Implementation of a broad coverage with MenB vaccine

Kaaijk et al. [4] discussed what should be taken into account to enable a successful implementation of a MenB vaccine with a broad coverage in national immunisation programmes. Epidemiology data, vaccine characteristics including vaccine coverage, immunogenicity, post-implementation surveillance and costs are relevant aspects that should be taken into account when selecting an appropriate immunisation strategy. The potential impact on strain variation and carriage, as well as monitoring vaccine-effectiveness, and rare but potentially serious adverse events are aspects that need to be included in a post-implementation surveillance plan.

6.4.5 International developments

4CMenB vaccine (Bexsero®, Novartis) was authorised for use by the European Medicines Agency in January 2013.
The Food and Drug Administration (FDA) has approved the use of 4CMenB vaccine (Bexsero®, Novartis) twice in response to MenB outbreaks at US college campuses. More than 5,000 students were vaccinated at Princeton University

and 20,000 students will be offered vaccination at the University of California Santa Barbara (http://www.cdc.gov/meningococcal/outbreaks/ucsb.html and http://www.cdc.gov/meningococcal/outbreaks/princeton.html).

The regional programme in Québec's Saguenay-Lac-Saint-Jean region is the first public campaign globally to offer Bexsero to all aged 2 months to 20 years. More than 45,000 infants, young children and adolescents (81%) have already received at least one dose of Bexsero (http://www.novartisvaccines.com/downloads/ newsroom/media-releases/640325.pdf).

In March 2014, the UK Joint Committee on Vaccination and Immunisation (JCVI) recommended that the 4CMenB vaccine (Bexsero®, Novartis) should be introduced into the NHS's routine immunisation schedule for children, provided that it can be obtained at a cost-effective price. Last year, however, JCVI concluded that, on the basis of the available evidence, routine infant or toddler immunisation using Bexsero® is highly unlikely to be cost-effective at any vaccine price based on the accepted threshold for cost-effectiveness used in the UK and could not therefore be recommended. After recalculation of the cost-effectiveness, the decision to recommend the introduction of 4CMenB in the routine immunisation schedule was made.
The vaccine will be administered at 2 and 4 months, with a booster at 12 months. There are no plans for a catch-up programme for older children, because the main burden of the disease is in young babies. (https://www.gov.uk/government/news/meningococcal-b-vaccination-programme-to-be-introduced). Furthermore, the JCVI advised that the vaccine should also be offered to 3 and 4 month-old neonates when it is introduced. The committee also stated that the new vaccine could cover some strains of meningococcal serogroup C causing meningitis and recommended the removal of the three-month dose of the group C meningococcal vaccine (note, in 2013 the second dose of the group C meningococcal vaccine at 4 months of age was removed), subject to the effective implementation of the group C meningococcal adolescent booster programme [Wise, 2014]. Currently in the UK and Ireland, stocks of the 4CMenB vaccine have been made available privately, allowing people who can afford it to obtain the vaccine. The vaccine is also available free of charge in the UK for people with medical conditions that increase their risk of MenB disease. In Ireland, the National Immunisation Advisory Committee is still in the process of deciding whether the vaccine will be made available to people with at-risk conditions free of charge. A decision is expected in 2014. (http://www.meningitis.org/menb-vaccine).
The impact of the 4CMenB/Bexsero on carriage is currently under evaluation in a multi-centre, controlled study among young adults (clinicalTrials.gov identifier NCT01214850). At cumulative sampling time points after vaccination, an impact on carriage of BCWY combined and any N. meningitides was observed. (http://www.slideshare.net/meningitis/1340-robert-c-read-28276214)
The immunogenicity and reactogenicity (see Chapter 4) of the 4CMenB vaccine in healthy children aged 4 years was assessed. Two hundred and nine serogroup B meningococcal (MenB) naive children aged 4 years were enrolled in the UK, Italy, Spain and the Czech Republic and they received two doses of 4CMenB administered 2 months apart. Blood samples were obtained at baseline and one month following the second dose. At baseline, less than 5% of the children had human complement serum bactericidal assay (hSBA) titers =1:5 for meningococci H44/76 (fHbp), 5/99 (NadA) and NZ98/254 (PorA), compared with 61% for M107013 (NHBA). This proportion was 91-100% one month after the second dose for all 4 strains. GMTs and 95% CIs one month after the second

dose were: 110 (99-122) for H44/76; 341 (301-388) for 5/99; 17 (14-19) for NZ98/254 and 48 (41-56) for M10713. It was concluded that 4CMenB is immunogenic at 4 years of age in this licensed schedule (presentation ESPID 2014: http://espid.meetingxpert.net/espid_945/poster_94730/ program.aspx/ anchor94730).
McQuaid et al. [5] showed that even with an additional booster dose with 4CMenB at 40 months of age, children immunized as infants with a 3-dose schedule at 6, 8 and 12 months showed variable waning of bactericidal antibodies by 5 years of age. This was also noted in children immunized for the first time with 2 doses at 40 and 42 months of age. The decrease in percentage of children with antibody titers above the putative protective threshold appeared to be strain-specific and therefore vaccine antigen-specific, with the greatest decline in immunity for strain NZ98/254 (PorA), whereas protection against strain 5/99 (NadA) was fully maintained.

Delbos et al. [6] analysed the impact of MenBvac, an outer membrane vesicle (OMV) vaccine against P1.7,16 strains, on meningococcal carriage. MenBvac vaccination appeared associated with lower carriage, i.e., 0.31% (1/321) among the vaccinated children versus 2.1% (16/761) among the non-vaccinated (p= 0.03).

The United States Food and Drug Administration (FDA) has granted Breakthrough Therapy designation to Pfizer’s vaccine candidate, bivalent rLP2086, currently under investigation for the prevention of invasive meningococcal disease due to Neisseria meningitides serogroup B in persons 10 – 25 years of age. A Breakthrough Therapy designation conveys FDA's existing fast track development programme features, as well as more intensive FDA guidance on an efficient drug development programme. The bivalent rLP2086 vaccine (Pfizer), containing one recombinant lipidated protein (rHbp) variant from each subfamily (A and B), is currently in phase 3 clinical development. This study assessed the safety (see Chapter 4) and immunogenicity of 2 or 3 doses of bivalent rLP2086 in healthy adolescents 11–18 years of age. The data using heterologous test strains indicate the importance of the additional response provided by a 3-dose regimen. Global phase 3 clinical trials with the bivalent rLP2086 vaccine are ongoing. This vaccine will be offered for licensing in the US for this age group (presentation at ESPID 2014).

6.4.6 *Tables and figures*

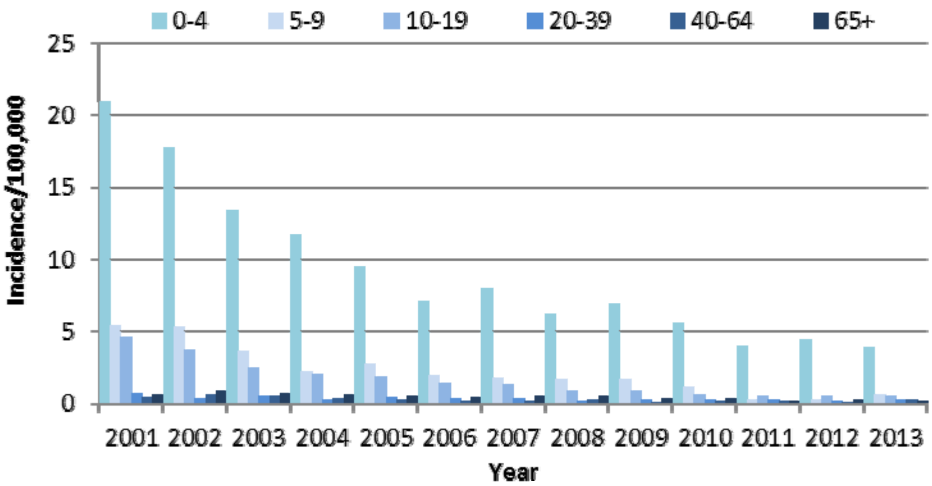

Figure 6.4.1 Age-specific incidence of MenB disease, 2001-2013

Table 6.4.1 Absolute numbers of invasive MenB isolates per age-category from 2001-2013

Age in yrs	**'01**	**'02**	**'03**	**'04**	**'05**	**'06**	**'07**	**'08**	**'09**	**'10**	**'11**	**'12**	**'13**
0-4	210	180	137	120	96	70	77	59	65	52	37	41	36
5-9	54	53	36	22	27	20	18	17	17	12	3	3	6
10-19	88	72	49	40	38	28	27	17	18	13	10	10	11
20-39	32	19	27	12	20	16	14	7	11	13	10	9	12
40-64	24	31	28	22	16	11	11	15	7	12	10	6	17
65+	14	20	16	15	12	10	12	13	8	10	5	7	6
Total	422	375	293	231	209	155	159	128	126	112	75	76	88

6.4.7 Literature

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6. McQuaid F, Snape MD, John TM, Kelly S, Robinson H, Houlden J, et al. Persistence of bactericidal antibodies to 5 years of age after immunization with serogroup B meningococcal vaccines at 6, 8, 12 and 40 months of age. The Pediatric Infectious Disease Journal. 2014;33(7):760-6.
7. Delbos V, Lemee L, Benichou J, Berthelot G, Deghmane AE, Leroy JP, et al. Impact of MenBvac, an outer membrane vesicle (OMV) vaccine, on the meningococcal carriage. Vaccine. 2013;31(40):4416-20.

6.5 Meningococcal non-serogroup B and C types

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

6.5.1 Key points

- In 2013, 22 (19%) meningoccocal cases were caused by non-serogroup B or C types from a total of 116 cases.
- Most non B and C meningocccocal cases were caused by serogroups W and Y, with respectively 7 and 14 cases in 2013.

6.5.2 Epidemiology

6.5.2.1 Meningococcal serogroup W

Since 2001, the number of meningococcal serogroup W (MenW) cases had decreased to 3-7 cases each year, except in 2011, which had only one case. In 2013, the number of MenW cases amounted to 7 (Figure 6.5.1 and Table 6.5.1).

6.5.2.2 Meningococcal serogroup Y

From 2001 to 2006, the number of MenY cases amounted to 4-7 cases each year. In 2007, the number of MenY cases had increased to 11 after which it decreased again to 7 in 2009. From 2010 to 2013, the number of MenY cases ranged from 12 to 15 cases each year (Figure 6.5.1 and Table 6.5.2).

6.5.2.3 Other meningococcal serogroups

In 2013, one Men29E case and no MenA/X/Z/non-groupable were reported.

6.5.3 Pathogen

There are no indications that the proportions of non-serogroup B or C strains isolated from patients with invasive disease in the Netherlands have changed.

6.5.4 International developments

Data from 33 European countries indicate that the emergence of serogroup Y observed since 2010 continued in 2012 in various regions of Europe, especially in Scandinavia. In Eastern and South-Eastern Europe, the relative proportion of serogroup Y remained low [1].

6.5.5 Tables and figures

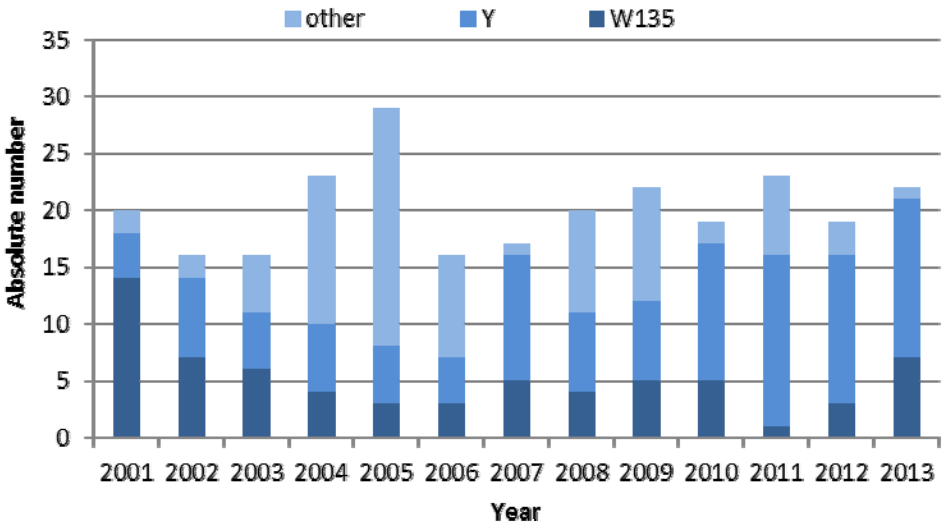

Figure 6.5.1 Absolute number of meningococcal non-serogroup B or C isolates (e.g. A, 29E, W, X, Y, Z, non-groupable), 2001-2013

Table 6.5.1 Absolute number of invasive MenW isolates per age category, 2001-2013

Age in yrs	**'01**	**'02**	**'03**	**'04**	**'05**	**'06**	**'07**	**'08**	**'09**	**'10**	**'11**	**'12**	**'13**
0-4	5	1	3	0	1	2	2	1	1	1	0	0	1
5-9	1	1	0	0	0	0	0	0	0	1	0	0	0
10-19	0	1	1	0	1	0	1	0	1	1	1	0	1
20-39	4	1	0	0	0	1	1	1	1	0	0	1	0
40-64	3	2	0	1	0	0	0	1	1	0	0	1	0
65+	1	1	2	3	1	0	1	1	1	2	0	1	5
Total	14	7	6	4	3	3	5	4	5	5	1	3	7

Table 6.5.2 Absolute number of invasive MenY isolates per age category, 2001-2013

Age in yrs	**'01**	**'02**	**'03**	**'04**	**'05**	**'06**	**'07**	**'08**	**'09**	**'10**	**'11**	**'12**	**'13**
0-4	0	0	1	0	0	0	0	0	1	1	0	2	2
5-9	0	0	0	1	0	0	1	0	0	0	1	3	0
10-19	0	1	1	2	0	0	1	0	0	2	5	1	1
20-39	1	2	1	0	0	0	1	1	1	3	2	2	0
40-64	1	0	1	1	2	0	2	2	2	3	3	3	3
65+	2	4	1	2	3	4	6	4	3	3	4	2	8
Total	4	7	5	6	5	4	11	7	7	12	15	13	14

6.5.6 Literature

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7 Other possible future NIP candidates

N.Y. Rots

7.1 Vaccines under development

An update of information with regard to vaccines for infectious diseases in development that have reached the clinical testing phase and are relevant for the Netherlands is given in Table 7.1. Relevant developments of combination vaccines are described in earlier chapters.

7.2 Tables and figures

Table 7.1 Vaccines for infectious diseases in development that have reached the clinical testing phase and are relevant for the Netherlands

Disease	Vaccine	status
Bacterial diseases		
Clostridium difficile	Toxoid vaccine (Sanofi Pasteur)	Placebo controlled phase II trial started 2013, FDA fast track designation
Helicobacter pylori	Recombinant vaccine	Phase I completed, limited protective immunity
Shigella	Live attenuated vaccine Poly saccharide-protein conjugate vaccine	Phase 2 completed Phase 1 ongoing
Staphylococcus Aureus		Phase 1 completed, but so far all human trials failed
Streptococcus group A & B	Conjugate vaccine	Phase II
Tuberculosis	GSK Mtb72F/AS02A	Phase II trial in 2-7 month-old infants completed
Viral diseases		
Cytomegalovirus (CMV)	gB/MF59 glycoprotein B vaccine DNA vaccine ASP0113 (Astellas Pharma)	gB/MF59: 50% reduction in CMV infection incidence in healthy postpartum females. Both vaccines limited the periods of viraemia
Epstein–Barr	Glycoprotein subunit vaccine and recombinant vaccine	Phase II
Hepatitis E	Recombinant protein vaccine	Phase III
Herpes simplex	Recombinant protein vaccine	Phase III
Parainfluenza	Cold adapted PIV3 attenuated, bovine attenuated PIV3	Phase II

Disease	**Vaccine**	**status**
RSV	live recombinant viral (chimeric) vector vaccine against RSV (F-protein) and parainfluenza (MEDI-534), live attenuated cold-passaged, temperature sensitive (*cpts*) cps2 vaccine, intranasal application, Subunit RSV vaccine, Recombinant viral vector vaccines, Recombinant live attenuated vaccines	Phase I or II trials in adults, healthy RSV and PIV3 seronegative children 6 to <24 months of age and 12-59 month-old seropositive children. In youngest age group, high percentage of children with nasal congestion
SARS	DNA plasmid expressing S-protein and inactivated viral vaccine	Phase I
Tick-borne encephalitis	Inactivated vaccine	Phase II

Source: Website of pharmaceutical companies and clinicaltrial.gov

List of abbreviations

4CMenB	multicomponent meningococcal B vaccine
ACIP	Advisory Committee on Immunisation Practices
AEFI	adverse events following immunisation
AFP	acute flaccid paralysis
AMC	Academic Medical Centre of Amsterdam
AOM	acute otitis media
aP	acellular pertussis
BES	Bonaire, Sint Eustatius and Saba, the Dutch Caribbean
bp	base pair
CAP	community acquired pneumonia
CBS	Statistics Netherlands
CDC	Centres for Disease Control and Prevention
CI	confidence interval
CIb	Centre for Infectious Disease Control
CMR	Continuous Morbidity Registration
CMV	Cytomegalovirus
CSF	cerebrospinal fluid
CVP	childhood vaccine providers
CWC	child welfare centres
DHD	Dutch Hospital data
DNA	desoxyribo nucleïnic acid
dPLY	detoxified pneumolysin
DTP	combination of diphtheria, tetanus, and pertussis vaccines
DVP	Department for Vaccine Supply and Prevention Programmes
ECDC	European Centre for Disease Control and Prevention
ELS	extensive limb swelling
EU	European Union
F	fusion
FDA	Food and Drug Administration
FHA	Filamentous haemagglutinin
fHbp	factor H binding protein
gE	glycoprotein E
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
HBV	hepatitis B virus
HC	Health Council
HCV	hepatitis C virus
HepB	hepatitis B virus
Hib	*Haemophilus influenzae* type b
HiP	nontypable *Heamophilus influenzae* and pneumococcal vaccine
HIV	human immunodeficiency virus
HN	haemagglutinin-neuraminidase
HPA	Health Protection Agency

HPV	human papillomavirus
hSBA	human complement serum bactericidal assay
ICD	International Classification of Diseases
ICER	Incremental cost effectiveness ratio
ICPC	International Classification of Primary Care
ICU	intensive care unit
IBD	invasivasive bacterial disease
IDS	Centre for Infectious Disease Research, Diagnostics and Screening
IPD	invasive pneumococcal disease
IPV	inactivated polio vaccine
IQR	interquartile range
JCVI	Joint Committee on Vaccination and Immunisation
JIM	Juvenile Immunisation with Meningococcal vaccine
LINH	the Netherlands Information Network of General Practice
LMR	National Medical Registration
MenACWY-CRM	quadrivalent meningococcal CMR conjugate vaccine
MenACWY-D	quadrivalent meningococcal diphtheria toxoid conjugate vaccine
MenACWY-TT	tetravalent meningococcal tetanus toxoid conjugate vaccine
MenA	Meningococcal serogroup A
MenB	Meningococcal serogroup B
MenC	Meningococcal serogroup C
MenW	Meningococcal serogroup W
MenY	Meningococcal serogroup Y
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
MSM	men who have sex with men
NadA	Neisserial adhesion A
NHBA	neisserial heparin binding antigen
NIP	national immunisation programme
NIVEL	Netherlands Institute for Health Services Research
NIVEL-PCD	NIVEL Primary Care Database
NKR	the Netherlands Cancer Registry
NPG	National Influenza Prevention Programme
NRBM	Netherlands Reference laboratory for Bacterial Meningitis
NTHi	nontypable *Haemophilus influenzae* strains
NVI	Netherlands Vaccine Institute
OMV	outer membrane vesicle
OPV	oral polio vaccine
PAHO	Pan American Health Organization
PASSYON	Papillomavirus Surveillance among STI clinic Youngsters
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PCV (VE)	proportion of cases vaccinated
PHI	public health institute
PHiD-CV	10-valent pneumococcal nontypeable Haemophilus influenza protein D conjugate vaccine
PhtD	pneumococcal histidine traid D
PIENTER	assessing immunisation effect to evaluate the NIP
PPV	proportion of population vaccinated
PPV	pneumococcal polysaccharides vaccine

Prn	Pertactin
PRP-T	*Haemophilus influenza* type b conjugate
QALY	quality-adjusted life year
QC	quality control
RIVM	National Institute for Public Health and the Environment, the Netherlands
RLB	reverse line-blot hybridisation
RSV	respiratory syncytial virus
RV	Rotavirus
SARS	Severe Acute Respiratory Syndrome
SH	small hydrophobic
SLE	Systemic lupus erythematodes
SPS	Singles Prevention Study
STI	sexually transmitted infections
Tdap	tetanus, diphtheria and pertussis vaccine
tIPV	trivalent inactivated polio vaccine
TNO	Netherlands Organisation for Applied Scientific Research
T-PEP	tetanus post-exposure prophylaxis
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 Organization
wP	whole-cell pertussis
WP	work package
ZonMW	The Netherlands Organisation for Health Research and Development

Appendix 1 Surveillance Methodology

Disease surveillance

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

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 has to be taken into account when following mortality trends.

Morbidity data

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 A1 for the period of notification for each disease [1].

Table A1 Periods of statutory notification for vaccine-preventable diseases (VPDs) included in the current National Immunisation Programme (NIP)

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 human papillomavirus (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 [2]. 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 Haemophilus influenzae type b (Hib) disease.

<u>Hospital admissions</u>
The National Medical Register (LMR) receives the discharge diagnoses of all patients who were 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 (DHD) 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 to underreporting, as shown by De Greeff et al. in a paper on meningococcal disease incidence [3].
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 [4] 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 causes other than poliovirus infection, are sometimes inadvertently registered as cases of acute poliomyelitis [4]. Thus, for poliomyelitis and tetanus, notifications are a more reliable source of surveillance.

<u>Laboratory data</u>
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 [5]. 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.

<u>Netherlands Reference Laboratory Bacterial Meningitis</u>
The Netherlands Reference Laboratory for Bacterial Meningitis (NRBM) is a collaboration between the National Institute for Public Health and the Environment (RIVM) and the Academic Medical Centre of Amsterdam (AMC). On a voluntary basis, microbiological laboratories throughout the Netherlands send isolates from the 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 invasive pneumococcal disease (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.

<u>NIVEL Primary care database</u>
Incidence rates of varicella and herpes zoster in general practice were calculated using data from routine electronic health records of general practitioners that are participating in NIVEL Primary Care Database (NIVEL-PCD), which incorporates the former LINH (Landelijk Informatie Netwerk Huisartsenzorg) that is maintained at the Netherlands Institute for Health Services Research (NIVEL). NIVEL-PCD uses routinely recorded data from health care providers to monitor health and the utilisation of health services in a representative sample of the Dutch population. All complaints and illnesses are recorded using the International Classification of Primary Care (ICPC-1). Annual incidence estimates of the total number of new episodes appearing in general practice in the Netherlands were made by extrapolating the reporting rates in these practices to the total number of Dutch residents, as obtained from Statistics Netherlands (CBS).

In 2012, there was a fourfold increase in the number of general practices participating in NIVEL-PCD compared with the previous group of LINH practices, resulting in a representative sample of 386 participating general practices with approximately 1.2 million registered patients (http://www.nivel.nl/NZR/zorgregistraties-eerstelijn). From 2012, incidence rates from NIVEL-PCD were calculated using an adjusted procedure: there were changes in definitions of episodes and in calculations of incidence, which caused an increase in the incidence for many diseases. Episode duration is defined by the time between the first and last consultation registered with the same code, and an additional period where patients are considered not susceptible (8 weeks for acute morbidities/complaints). Incidence rates are calculated by using a more specific selection of patient years [6]. Because of these changes, we decided to report previously published incidences based on the old method until 2011 [7], and incidence rates using the new method starting in 2012 [8]. Due to the new estimation method, the data for 2012 (based on 219 practices) are not comparable to previous years. To be able to detect changes in the incidence in recent years, we therefore decided to include data from a selection of 74 practices that consistently recorded good quality data in the period 2010-2012 as well.
At this moment, the length of the episode duration of 8 weeks is still under discussion, especially for herpes zoster. A final decision is expected by the end of 2014. Changing the episode duration will influence the height of the incidence; so, if necessary, data for 2012 will be corrected in the next report.

<u>Virological laboratories</u>
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 bear 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.

Vaccine effectiveness

After implementation of a vaccination into the NIP, vaccine-effectiveness (VE) can be routinely estimated using the ‘screening method’ with the following equation:

VE (%) = 1- [PCV / (1-PCV) * (1-PPV/PPV], in which 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 [9].

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.

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 from the general population of the Netherlands is periodically asked to donate a blood sample and fill in a questionnaire (PIENTER survey). This survey was performed in 1995–1996 (nblood=10,128) [10] and in 2006–2007 (nblood=7,904) [11]. Oversampling of people living in regions with low vaccine coverage and of immigrants is done to gain greater insight into differences in immunity among specific groups.

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) [12].

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 [13]. From 1 January 2011 on, 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, in 2011 Lareb started a campaign among parents of vaccinated children to promote the reporting of AEFIs.
In addition, the Centre for Infectious Disease Control (CIb) of the RIVM conducts systematic studies to monitor the safety of the NIP, e.q. questionnaire surveys and linkage studies between different databases.

Cost-effectiveness

The decision to include a certain vaccination option in the national immunisation programme relies upon several factors, including vaccine safety and efficacy, the avertable disease burden, acceptability, and the cost-effectiveness of vaccination. Cost-effectiveness is defined as the additional cost per additional unit of health benefit produced as compared with an alternative, such as the vaccine already in use or no vaccination. In other words, an economic evaluation of a vaccination programme provides information on whether the health gain associated with a new vaccine is worth the cost, as compared with other options for spending on health improvements or prevention. Most commonly, cost-effectiveness is expressed in cost per quality-adjusted life years (QALY), which is a measure of disease burden, comprising both the quality and the quantity of life. If provided in a transparent and standardised way, evidence of the cost-effectiveness can contribute to policy recommendations for vaccinations in the national immunisation programme.

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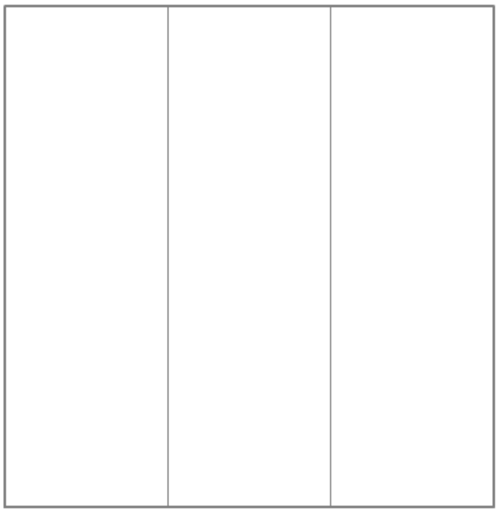
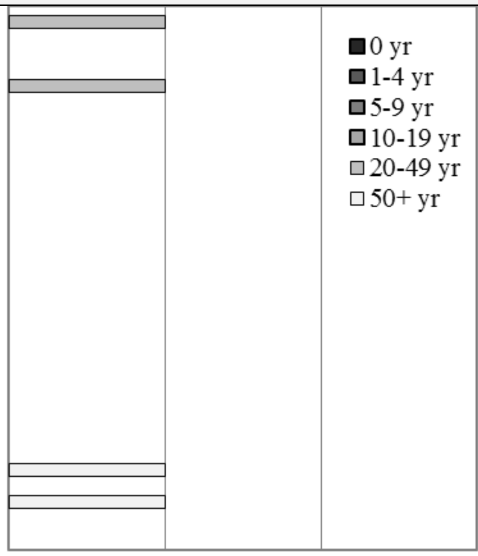
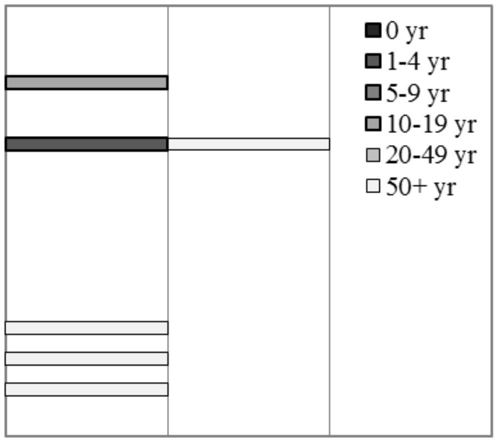
Appendix 2 Mortality and morbidity figures

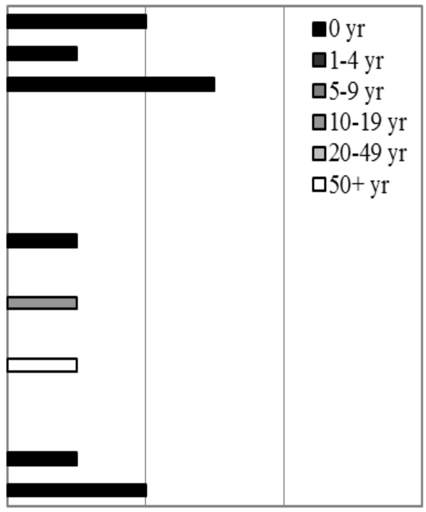
Diphtheria								**ICD9: 032** **ICD10: A36**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Mortality								
1997	0	0	0	0	0	0	**0**	
1998	0	0	0	0	0	0	**0**	
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	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**	
2013	0	0	0	0	0	0	**0**	

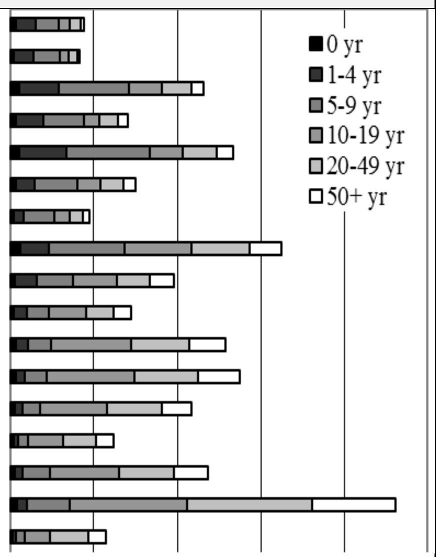




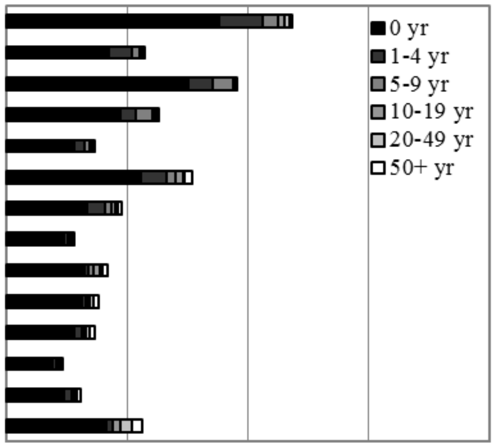
Diphtheria								ICD9: 032 ICD10: A36
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Hospitalisations								
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	1	0	0	**1**	
2002	0	0	0	0	0	0	**0**	
2003	0	1	0	0	0	1	**2**	
2004	0	0	0	0	0	0	**0**	
2005	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**	
Laboratory diagnoses								
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**	
2013	0	0	0	0	3	0	**3**	

Pertussis								**ICD9: 033** **ICD10: A37**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
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**	
2013	77	136	317	890	1,394	605	**3,419**	

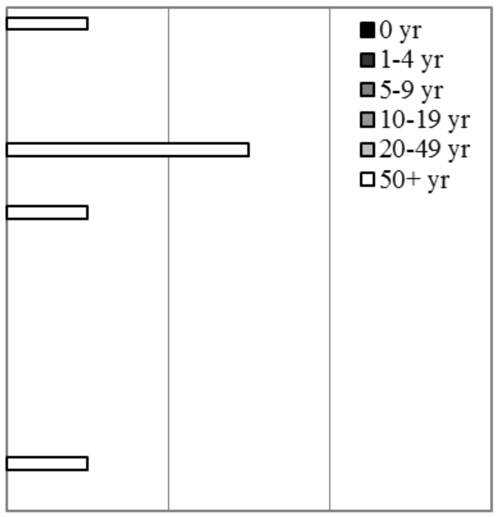


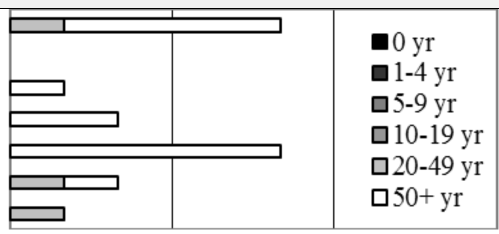


Pertussis								**ICD9: 033** **ICD10: A37**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Hospitalisations								
1999	352	73	24	12	8	5	**474**	
2000	171	37	12	5	0	5	**230**	
2001	302	40	33	1	2	3	**381**	
2002	190	25	27	4	3	3	**252**	
2003	114	16	9	2	2	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**	

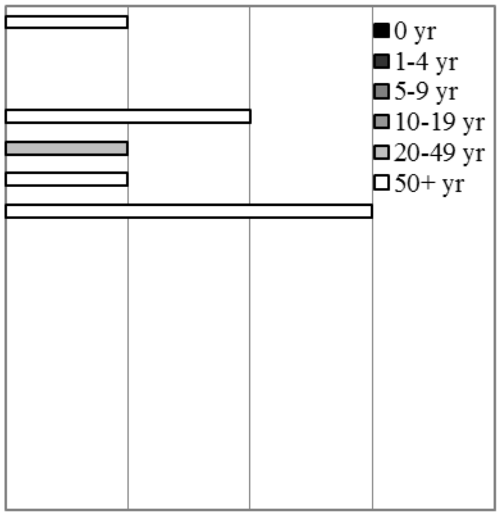


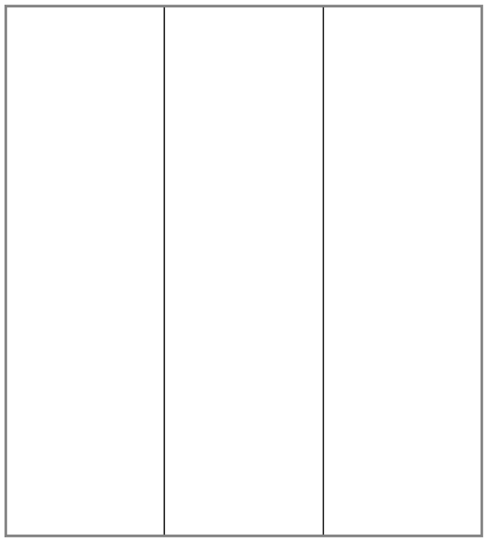
Tetanus								**ICD9: 037, 7713** **ID10: A33-35**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Mortality								
1997	0	0	0	0	0	1	**1**	
1998	0	0	0	0	0	0	**0**	
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	3	**3**	
2002	0	0	0	0	0	0	**0**	
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**	
2013	0	0	0	0	1	0	**1**	



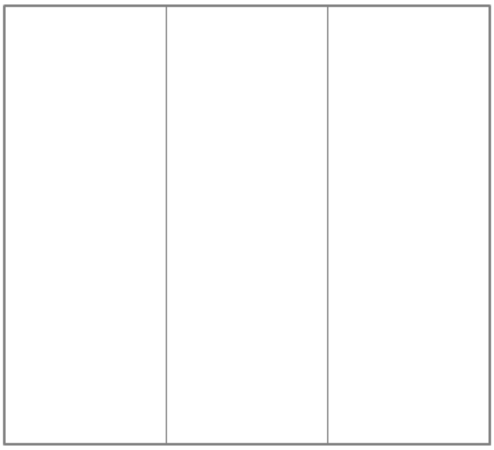


Poliomyelitis								**ICD9: 045** **ICD10: A80**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Mortality (acute)								
1997	0	0	0	0	0	1	**1**	
1998	0	0	0	0	0	0	**0**	
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	2	**2**	
2001	0	0	0	0	1	0	**1**	
2002	0	0	0	0	0	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**	
2013	0	0	0	0	0	0	**0**	

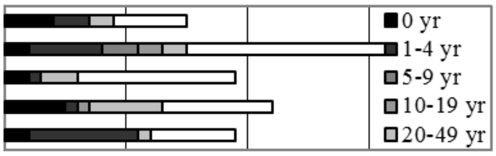


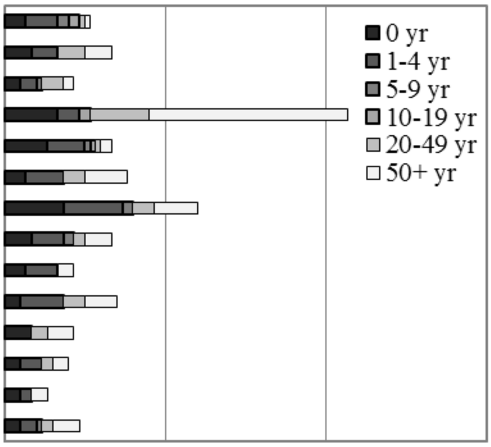


Poliomyelitis								**ICD9: 045** **ICD10: A80**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Hospitalisations								
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	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**	



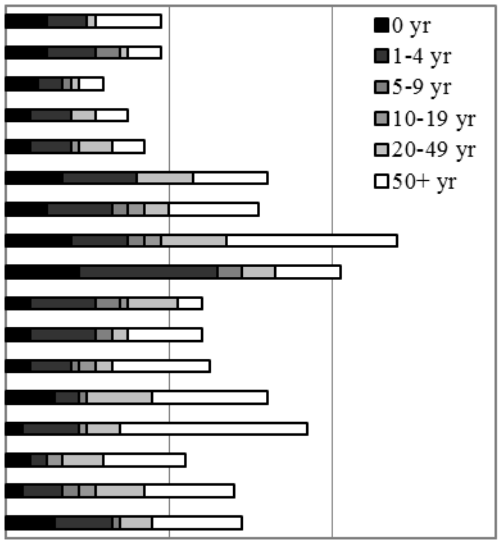
***Haemophilus influenzae* type b**								**ICD9: 3200** **ICD10: A41.5, G00.0**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
*Notifications**								
2009	4	3	0	0	2	6	**15**	
2010	2	6	3	2	2	17	**32**	
2011	2	1	0	0	3	13	**19**	
2012	5	1	0	1	6	9	**22**	
2013	2	9	0	0	1	7	**19**	
*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**	

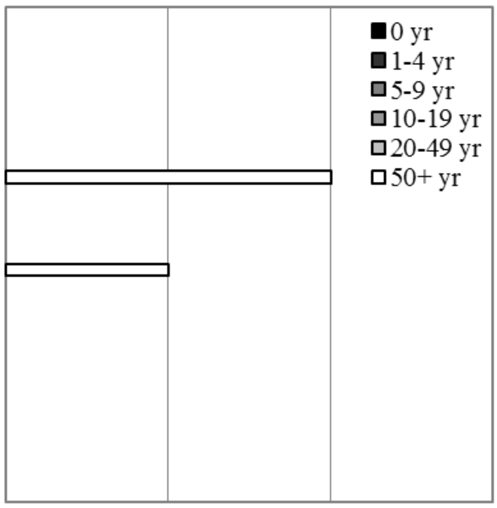


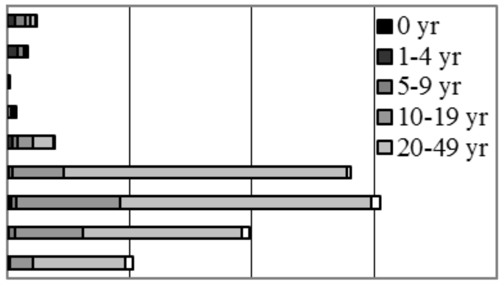
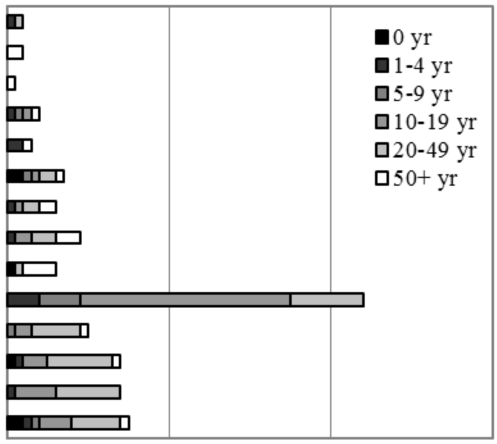
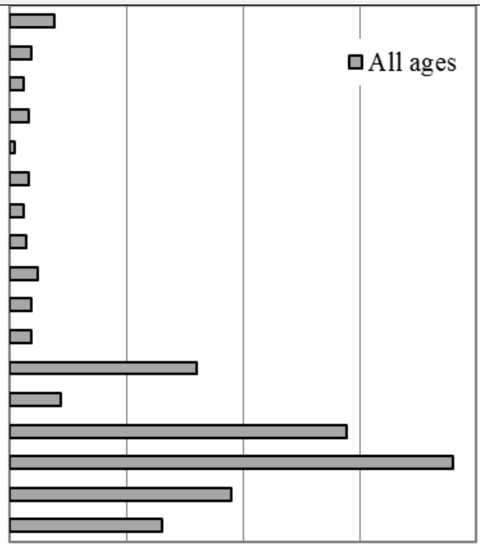


*Notifiable since 2009

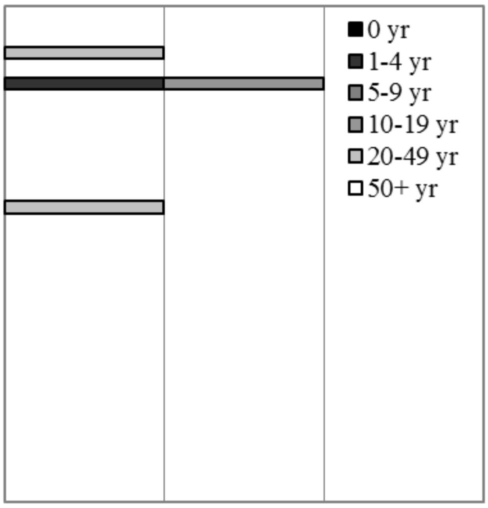
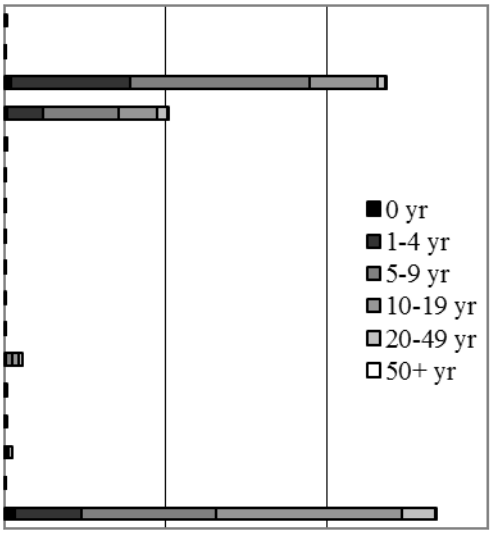
**For one patient the age is unknown

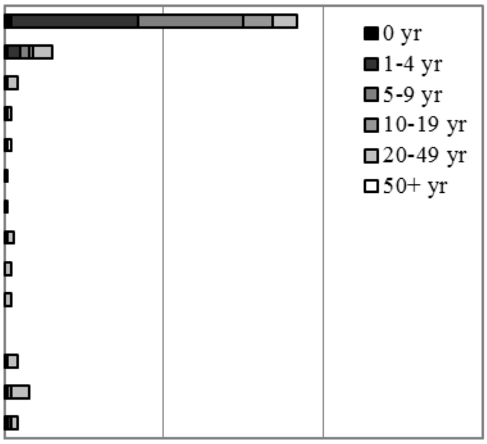
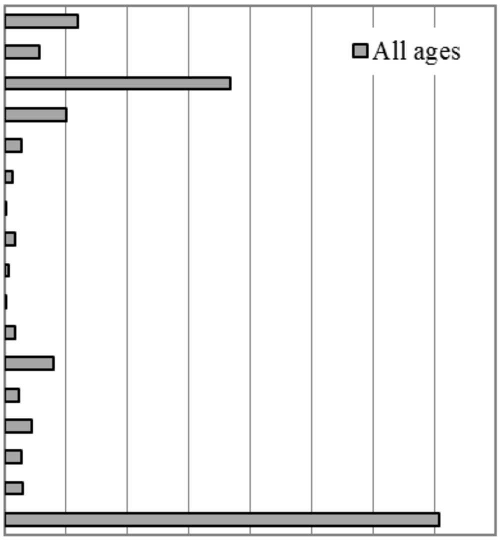
***Haemophilus influenzae* type b**								ICD9: 3200 ICD10: A41.5, G00.0
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Isolates								
1997	5	5	0	0	1	8	**19**	
1998	5	6	3	0	1	4	**19**	
1999	4	3	1	0	1	3	**12**	
2000	3	5	0	0	3	4	**15**	
2001	3	5	0	1	4	4	**17**	
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**	
2013	6	7	1	0	4	11	**29**	

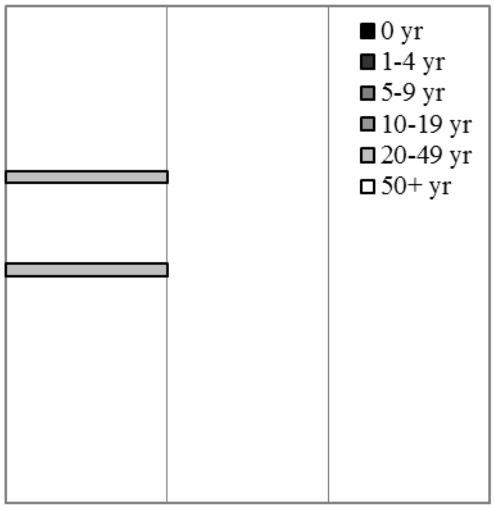
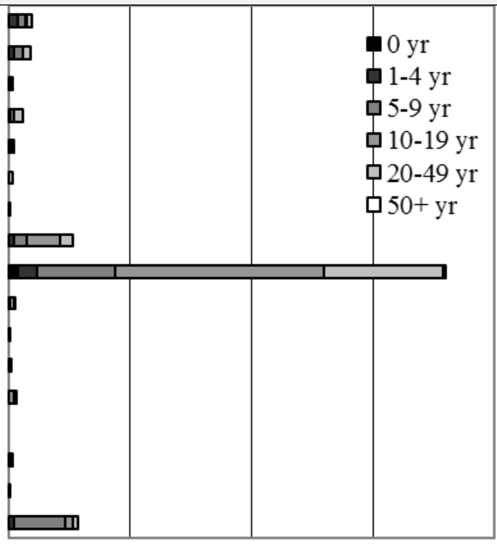
Mumps								ICD9: 072 ICD10: B26
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Mortality								
1997	0	0	0	0	0	0	**0**	
1998	0	0	0	0	0	0	**0**	
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	2	**2**	
2003	0	0	0	0	0	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**	

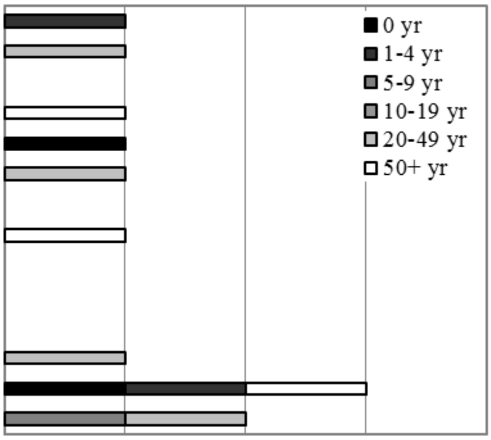
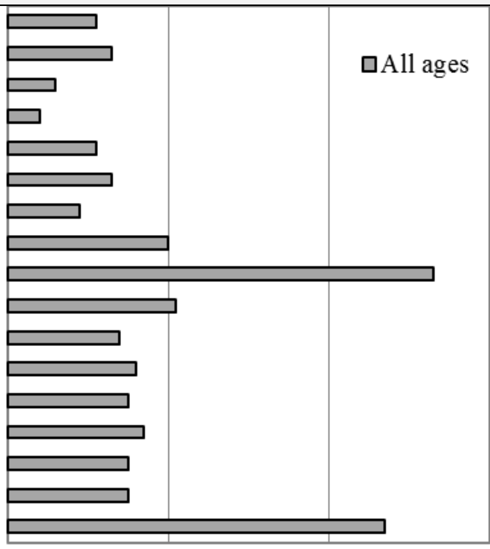
Mumps								**ICD9: 072 / ICD10: B26**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Notifications								
1997	0	14	16	9	7	1	**47**	
1998	0	17	10	1	2	4	**34**	
1999*	0	0	3	0	1	0	**4**	
2008*	0	1	5	5	2	1	**14**	
2009	0	9	8	26	33	2	**78**	
2010	0	3	6	84	463	6	**562**	
2011	2	5	9	168	410	15	**609**	
2012	0	2	12	110	260	13	**397**	
2013	0	3	2	37	152	11	**205**	
Hospitalisations								
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**	
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**	
2013	-	-	-	-	-	-	**65**	

*No notifications between 1 April 1999 and 31 December 2008

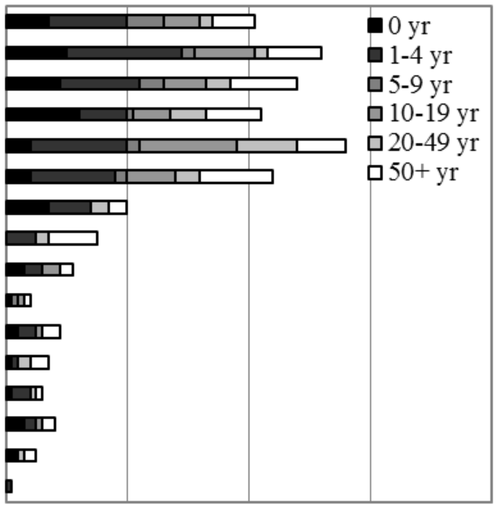
Measles								**ICD9: 055** **ICD10: B05**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Mortality								
1997	0	0	0	0	0	0	**0**	
1998	0	0	0	0	1	0	**1**	
1999	0	1	0	1	0	0	**2**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	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**	
2013	68	412	834	1155	199	9	**2,677**	

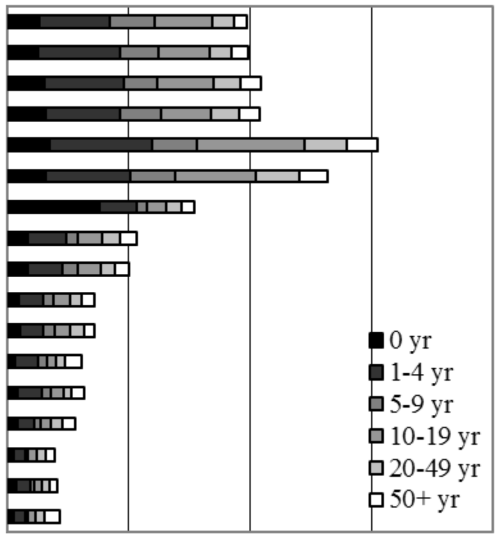
Measles								**ICD9: 055** **ICD10: B05**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Hospitalisations								
1999	2	40	33	9	8	0	**92**	
2000	1	4	3	1	6	0	**15**	
2001	1	0	0	0	3	0	**4**	
2002	0	0	0	1	1	0	**2**	
2003	0	1	0	0	0	1	**2**	
2004	0	0	0	1	0	0	**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**	
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**	
2013	-	-	-	-	-	-	**212**	

Rubella (Acquired)								ICD9: 056 ICD10: B06
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
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**	
2013	0	5	42	6	4	0	**57**	

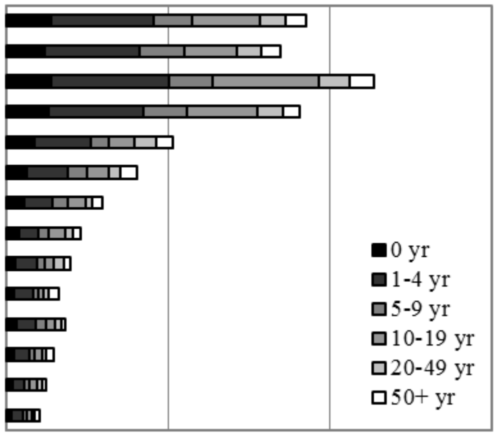
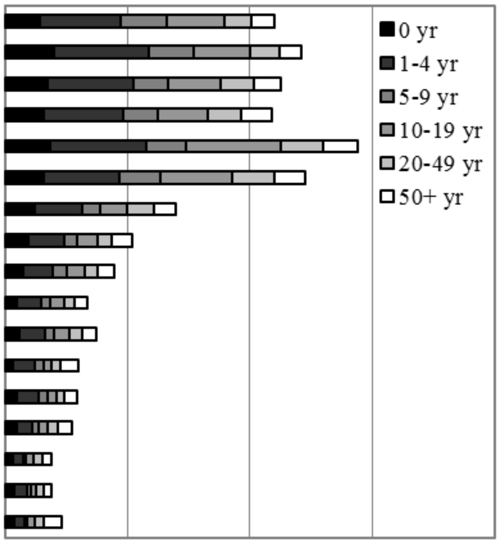
Rubella (Acquired)								**ICD9: 056** **ICD10: B06**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Hospitalisations								
1999	0	1	0	0	0	0	**1**	
2000	0	0	0	0	1	0	**1**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	1	**1**	
2003	1	0	0	0	0	0	**1**	
2004	0	0	0	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**	
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**	
2013	-	-	-	-	-	-	**47**	

Meningococcal disease								ICD9: 036.0-4, 036.8-9 ICD10: A39
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
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	31	7	15	17	16	**104**	
2013	15	23	6	14	20	31	**109**	



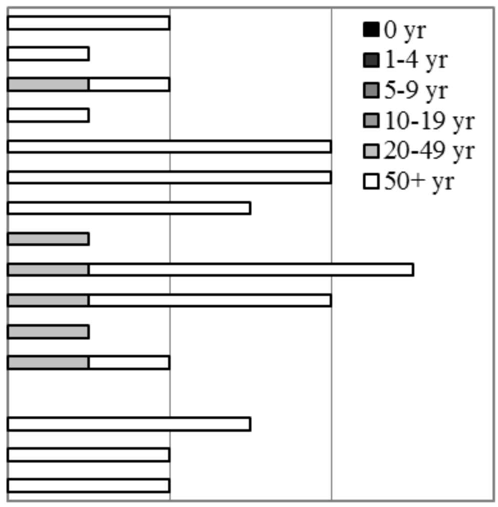
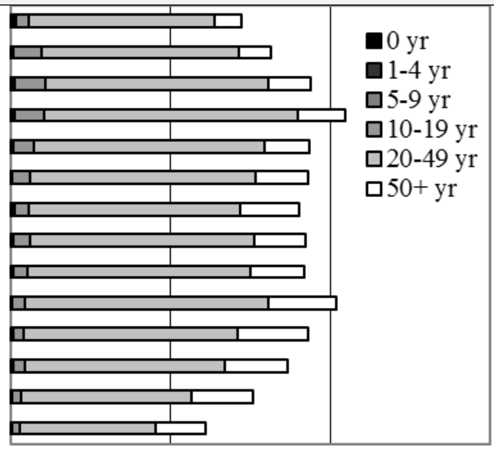


*For nine patients the age is unknown

Meningococcal disease								ICD9: 036.0-4, 036.8-9 ICD10: A39
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
*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**	
*Isolates***								
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**	
2013	19	21	6	14	19	37	**116**	

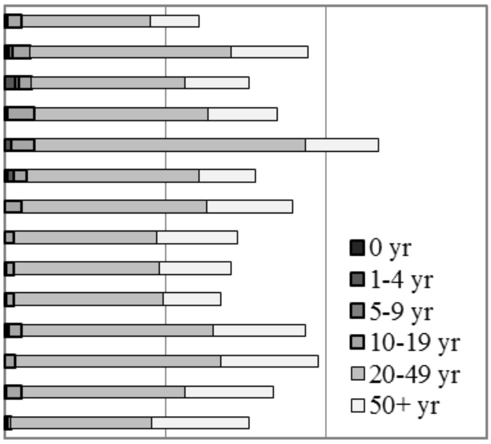
*For 9 patients the age is unknown

**Nontypeables excluded

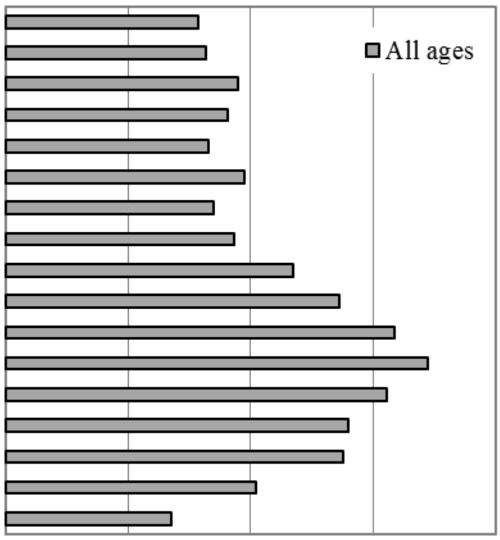
Hepatitis B								**ICD9: 070.2-3** **ICD10: B16, B17.0, B18.0, B18.1**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Mortality (B16; Acute)								
1997	0	0	0	0	0	2	**2**	
1998	0	0	0	0	0	1	**1**	
1999	0	0	0	0	1	1	**2**	
2000	0	0	0	0	0	1	**1**	
2001	0	0	0	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**	
2013*	0	2	6	52	850	311	**1,254**	

*For 33 patients the age is unknown

Hepatitis B								**ICD9: 070.2-3** **ICD10: B16, B17.0, B18.0, B18.1**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
*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**	

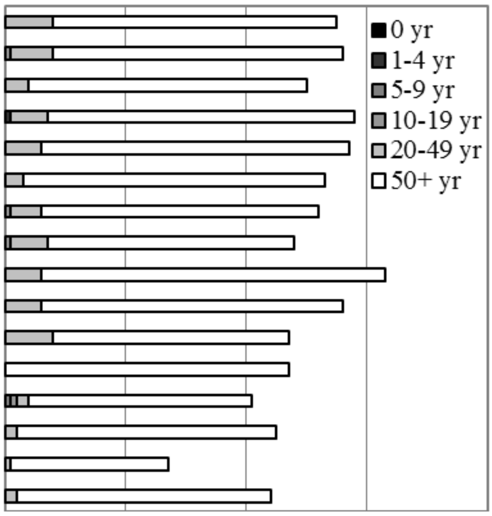


Laboratory diagnoses								
1997	-	-	-	-	-	-	**787**	
1998	-	-	-	-	-	-	**819**	
1999	-	-	-	-	-	-	**950**	
2000	-	-	-	-	-	-	**904**	
2001	-	-	-	-	-	-	**827**	
2002	-	-	-	-	-	-	**974**	
2003	-	-	-	-	-	-	**849**	
2004	-	-	-	-	-	-	**932**	
2005	-	-	-	-	-	-	**1,174**	
2006	-	-	-	-	-	-	**1,361**	
2007	-	-	-	-	-	-	**1,588**	
2008	-	-	-	-	-	-	**1,725**	
2009	-	-	-	-	-	-	**1,553**	
2010	-	-	-	-	-	-	**1,401**	
2011	-	-	-	-	-	-	**1,377**	
2012	-	-	-	-	-	-	**1,020**	
2013	-	-	-	-	-	-	**676**	

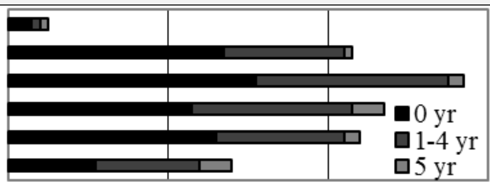


*For 27 patients the age is unknown

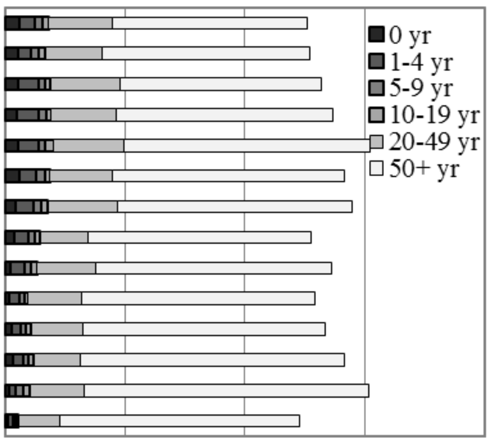
Pneumococcal disease								**ICD9: 0382, 481, 4823, 3201** **ICD10: J13, 18.0, 18.9, G00.1, A40.4**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Mortality (J13; Pneumonia)								
1997	0	0	0	0	8	47	**55**	
1998	0	0	0	1	7	48	**56**	
1999	0	0	0	0	4	46	**50**	
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**
2013	11	13	4*	-	-	-	**28**



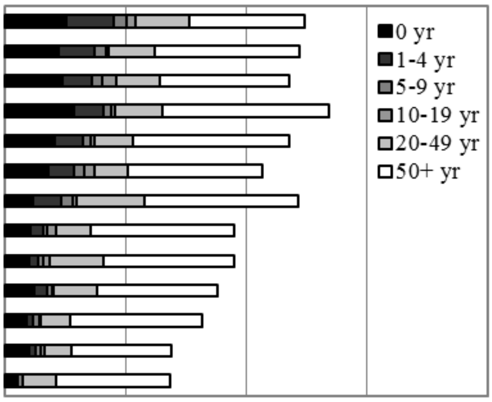
Hospitalisations**							
1999	124	126	63	52	529	1,622	**2,521**
2000	113	110	60	53	476	1,727	**2,544**
2001	108	170	53	48	576	1,676	**2,638**
2002	97	188	61	42	544	1,796	**2,734**
2003	109	171	56	71	587	2,047	**3,057**
2004	120	144	66	44	523	1,930	**2,832**
2005	94	146	68	51	580	1,951	**2,899**
2006	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**



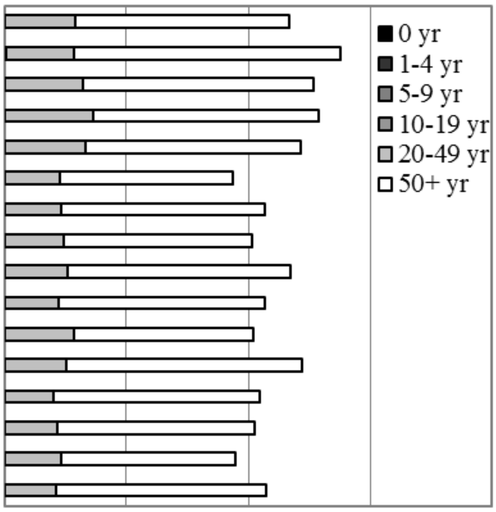
*Notifiable for 0 to 5 year-old children

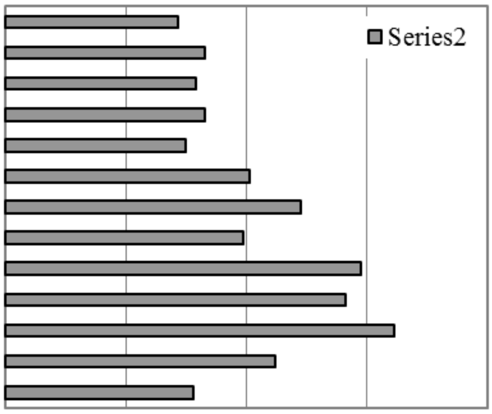
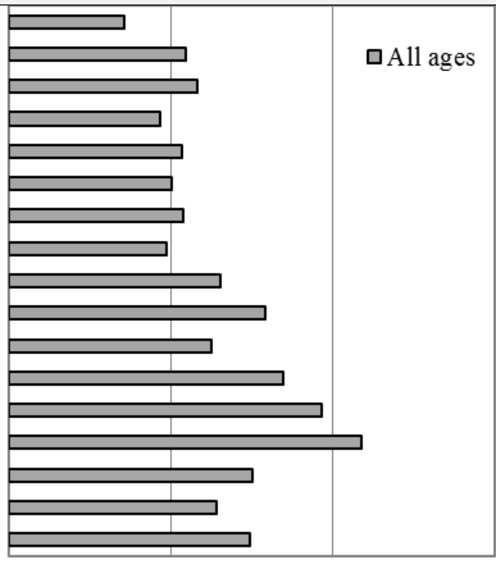
**For 91 patients the age is unknown

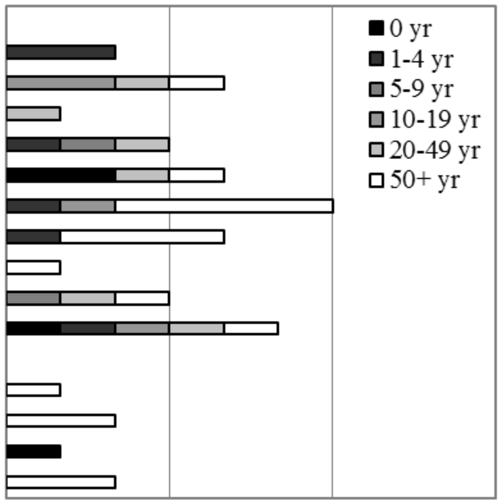
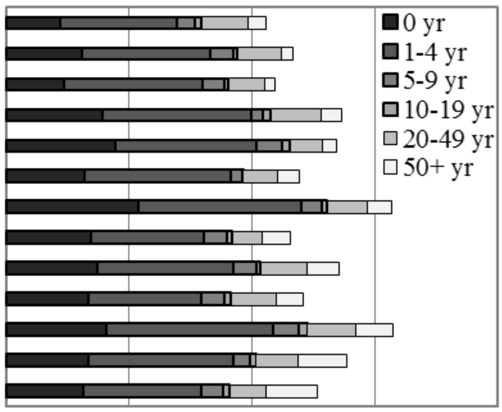
Pneumococcal disease								ICD9: 0382, 481, 4823, 3201 ICD10: J13, 18.0, 18.9, G00.1, A40.4
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Isolates (meningitis)								
2001	51	39	11	7	45	95	**248**	
2002	45	30	9	2	38	120	**244**	
2003	48	24	9	11	37	107	**236**	
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**	
2013	9	2	4	0	28	94	**137**	



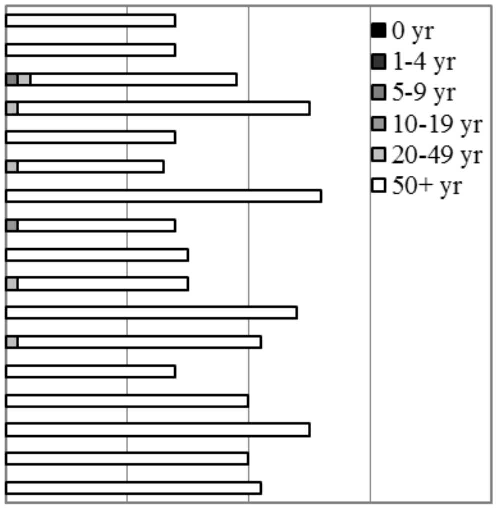
Human papillomavirus								ICD10: C53
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Mortality (Cervical cancer)								
1997	0	0	0	0	58	176	**234**	
1998	0	0	0	1	56	219	**276**	
1999	0	0	0	0	64	189	**253**	
2000	0	0	0	0	73	185	**258**	
2001	0	0	0	0	66	177	**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**	



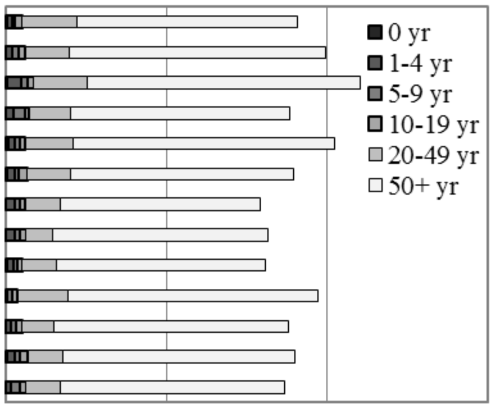
Rotavirus								
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Hospitalisations (estimation)								
2000	-	-	-	-	-	-	**2,864**	
2001	-	-	-	-	-	-	**3,312**	
2002	-	-	-	-	-	-	**3,160**	
2003	-	-	-	-	-	-	**3,322**	
2004	-	-	-	-	-	-	**3,000**	
2005	-	-	-	-	-	-	**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	-	-	-	-	-	-	**1,692**	
2009	-	-	-	-	-	-	**1,936**	
2010	-	-	-	-	-	-	**2,180**	
2011	-	-	-	-	-	-	**1,504**	
2012	-	-	-	-	-	-	**1,287**	
2013	-	-	-	-	-	-	**1,487**	

Varicella (Chickenpox)								**ICD9: 052** **ICD10: B01**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
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**	

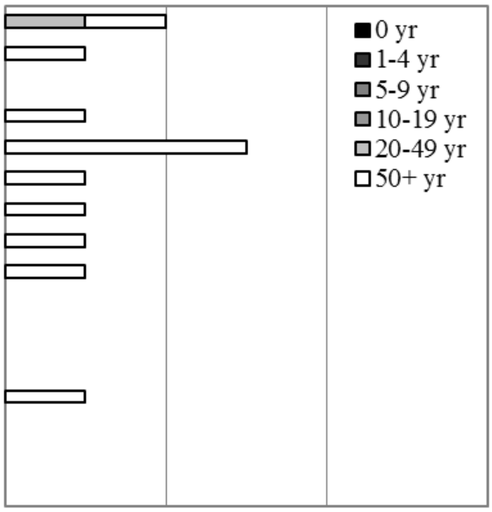
Herpes zoster (Shingles)								**ICD9: 053** **ICD10: B02**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
Mortality								
1997	0	0	0	0	0	14	**14**	
1998	0	0	1	0	1	17	**19**	
1999	0	0	0	0	1	24	**25**	
2000	0	0	0	0	0	14	**14**	
2001	0	0	0	0	1	12	**13**	
2002	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**	

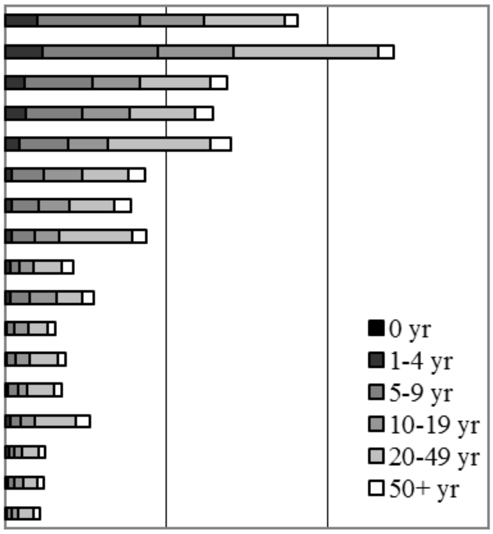


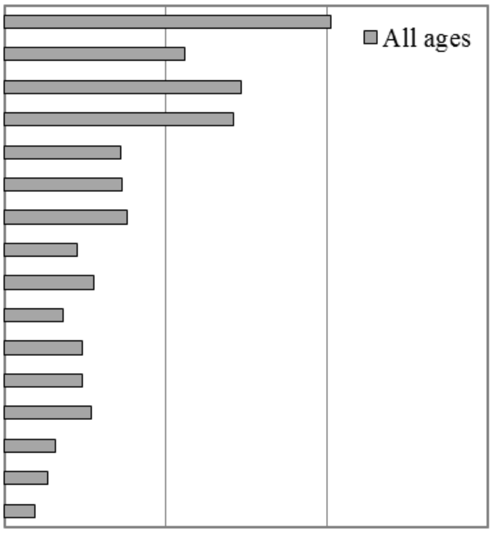
Hospitalisations								
2000	2	6	4	9	68	274	**363**	
2001	1	8	7	9	55	319	**399**	
2002	2	18	7	8	67	340	**442**	
2003	1	9	14	6	51	273	**354**	
2004	4	8	6	7	60	324	**409**	
2005	2	9	5	11	54	278	**359**	
2006	0	11	7	7	43	249	**317**	
2007	1	10	7	8	33	267	**326**	
2008	2	8	5	6	43	259	**323**	
2009	0	2	6	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								**ICD10: B15**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
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**	
2013	0	7	16	18	48	20	**109**	





Hepatitis A								**ICD10: B15**
Year	**Age (years)**						**Total**	**N**
	0	**1-4**	**5-9**	**10-19**	**20-49**	**50+**		
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**	
2013	-	-	-	-	-	-	**38**	

Appendix 3 Overview of changes in the NIP since 2000

Date	Injection	Age	Old vaccine	New vaccine	Introduced for children born on or after[1]
1 July 2001	aP	4 years	-	Acellular pertussis vaccine/GSK	1 January 1998
1 September 2002	MenC	14 months	-	NeisVac-C/Baxter	1 June 2001 (catch-up campaign in June 2002 for birth cohorts 1 June 1983 to 31 May 2001)
1 March 2003	DTwP-IPV/Hib	2, 3, 4 and 11 months	DTwP-IPV vaccine/NVI and Hib vaccine/NVI	DTwP-IPV/Hib vaccine/NVI	1 April 2002
	HBV	2, 3, 4 and 11 months	-	HBVAXPRO/SP MSD	1 January 2003 (specific risk groups[2])
1 January 2005	DTaP-IPV/Hib	2, 3, 4 and 11 months	DTwP-IPV/Hib vaccine/NVI	Infanrix IPV+Hib/GSK	1 February 2004
1 January 2006	HBV	At birth	-	HBVAXPRO/SP MSD	1 January 2006 (specific risk groups[3])
	DTaP-IPV/Hib	2, 3, 4 and 11 months	Infanrix IPV+Hib/GSK	Pediacel/SP MSD	1 February 2005
1 June 2006	Pneumo	2, 3, 4 and 11 months	-	Prevenar/Wyeth	1 April 2006
	DTaP-HBV-IPV/Hib	2, 3, 4 and 11 months	Pediacel/SP MSD	Infanrix hexa/GSK	1 April 2006 (specific risk groups[2])
July/August 2006	DTaP-IPV	4 years	DT-IPV vaccine/NVI and Acellular pertussis vaccine/GSK	Traxis Pollo/SP MSD	July/August 2002
September/October 2006	MMR	14 months	MMR vaccine/NVI	MMR VaxPro/SP MSD / Priorix/GSK	July/August 2005
1 January 2008	HBV	At birth	HBVAXPRO/SP MSD	HBVAXPRO/SP MSD	1 January 2008 (specific risk groups[4])
1 February 2008	DTaP-IPV	4 years	Traxis Pollo/SP MSD[5]	Infanrix IPV/GSK	1 February 2004
1 July-mid December 2008	DTaP-HBV-IPV/Hib	2, 3, 4 and 11 months	Pediacel/SP MSD	Infanrix IPV+Hib/GSK	1 August 2007

Date	Injection	Age	Old vaccine	New vaccine	Introduced for children born on or after[1]
1 September 2008	HBV	At birth	HBVAXPRO/SP MSD	Engerix-B Junior/GSK	1 September 2008 (specific risk groups[4])
	MMR	9 years	MMR vaccine/NVI	Priorix/GSK	1 September 1999
October 2008	MMR	9 years	Priorix/GSK	MMR VaxPro/SP MSD / Priorix/GSK	1 October 1999
1 January 2010	HPV	12 years[6]	-	Cervarix/GSK	1 January 1997 (catch-up campaign in 2009 for birth cohorts 1 January 1993 to 31 December 1996)
	DTaP-IPV/Hib	2, 3, 4 and 11 months	Pediacel/SP MSD / Infanrix IPV+Hib/GSK	Pediacel/SP MSD	1 February 2009
1 May 2011	Pneumo	2, 3, 4 and 11 months	Prevenar/Wyeth	Synflorix/GSK	1 March 2011
1 October 2011	DTaP-HBV-IPV/Hib	2, 3, 4 and 11 months	Pediacel/SP MSD	Infanrix hexa/GSK	1 August 2011
1 December 2013	Pneumo	2, 4 and 11 months	Synflorix/GSK	Synflorix/GSK	1 October 2013
1 January 2014	HPV	12 years[7]	Cervarix/GSK	Cervarix/GSK	1 January 2001

[1] The birth cohort from which children received at least one injection of the newly introduced vaccination.

[2] 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.

[3] Only for children whose mother tested positive for HBsAg.

[4] Only for children whose mother tested positive for HBsAg and children with Down syndrome.

[5] Used until March 2008.

[6] Only girls were vaccinated and received three doses of HPV vaccine: at 0, 1 and 6 months.

[7] Only girls were vaccinated and received two doses of HPV vaccine: at 0 and 6 months.

Appendix 4 Composition of vaccines used in 2013-2014

Vaccine	Composition
Pediacel/SP MSD RVG 32118 Diphtheria, tetanus, 5 component acellular pertussis vaccine, inactivated poliomyelitis vaccine and conjugated *Haemophilus influenzae* type b-vaccin (adsorbed) 0.5 ml	Purified diphtheria toxoid > 30 IU Purified tetanus toxoid > 40 IU Purified pertussis toxoid (PT) 20 µg Purified filamentous haemagglutinin (FHA) 20 µg Purified fimbrial agglutinogens 2 and 3 (FIM) 5 µg Purified pertactin (PRN) 3 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU *Haemophilus influenzae* type b polysaccharide (polyribosylribitol phosphate) 10 µg conjugated to tetanus toxoid (PRP-T) 20 µg absorbed to aluminium phosphate 1.5 mg
DT-IPV vaccine/NVI RVG 17641 Diphtheria (adsorbed), tetanus (adsorbed) and inactivated poliomyelitis vaccine 1 ml	Diphtheria-toxoid* > 5 IU Tetanus toxoid* > 20 IU Inactivated poliovirus type 1 > 40 DU Inactivated poliovirus type 2 > 4 DU Inactivated poliovirus type 3 > 7.5 DU *adsorbed to aluminium phosphate 1.5 mg Al3+
Synflorix/GSK EU/1/09/508 Pneumococcal polysaccharide conjugate vaccine (adsorbed) 0.5 ml	Pneumococcal polysaccharide serotype 1[1,2] 1 µg Pneumococcal polysaccharide serotype 4[1,2] 3 µg Pneumococcal polysaccharide serotype 5[1,2] 1 µg Pneumococcal polysaccharide serotype 6B[1,2] 1 µg Pneumococcal polysaccharide serotype 7F[1,2] 1 µg Pneumococcal polysaccharide serotype 9V[1,2] 1 µg Pneumococcal polysaccharide serotype 14[1,2] 1 µg Pneumococcal polysaccharide serotype 18C[1,3] 3 µg Pneumococcal polysaccharide serotype 19F[1,4] 3 µg Pneumococcal polysaccharide serotype 23F[1,2] 1 µg [1]absorbed to aluminium phosphate 0.5 mg Al3+ [2]conjugated to protein D (obtained from non-typable *Haemophilus influenzae*) carrier protein 9-16 mg [3]conjugated to tetanus toxoid 5-10 mg [3]conjugated to diphtheria toxoid 3-6 mg
NeisVac-C/Baxter RVG 26343 Conjugated meningococcal C saccharide vaccine (adsorbed) 0.5 ml	Neisseria meningitidis (C11-strain) Polysaccharide O-deacetylated 10 µg conjugated to tetanus toxoid 10-20 µg adsorbed to aluminium hydroxide 0.5 mg Al^{3+}

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

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

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