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 2014-2015

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## Surveillance and developments in 2014-2015

RIVM Report 2015-0134

## Colophon



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# Contents

# Publiekssamenvatting

## Het Rijksvaccinatieprogramma in Nederland

*Surveillance en ontwikkelingen in 2014-2015*

In Nederland is de vaccinatiegraad binnen het Rijksvaccinatieprogramma (RVP) hoog, waardoor weinig mensen de ziekten krijgen waartegen zij worden ingeënt. Alleen de deelname aan de vaccinatie van meisjes tegen het humaan papillomavirus (HPV) ligt lager. Na de vaccinaties komen weinig ernstige bijwerkingen voor. Bijwerkingen die gerapporteerd worden zijn doorgaans niet ernstig van aard zijn. Continue monitoring is nodig om een optimaal vaccinatieprogramma te behouden.

### Wijzigingen in het vaccinatieschema in 2014-2015

Sinds januari 2014 is de vaccinatie tegen het HPV-virus, dat baarmoederhalskanker kan veroorzaken, teruggebracht naar twee prikken. De vaccinatie wordt aan alle twaalfjarige meisjes aangeboden.

### Ontwikkelingen voor RVP-ziekten

Door de uitbreiding van het pneumokokkenvaccin met drie typen in 2011 is het aantal kinderen gedaald dat van deze drie typen ziek werd. Deze daling was ook te zien onder volwassenen, die mogelijk indirect door de vaccinatie van kinderen zijn beschermd.
Kinkhoest nam in 2014 weer toe na een daling in 2013. Het aantal zieken was minder hoog dan tijdens de epidemie in 2012. De bof kwam weinig voor in 2014, al steeg het aantal meldingen weer in de eerste maanden van 2015. De meeste mazelengevallen zijn in de eerste twee maanden van 2014 gerapporteerd, aan het einde van de epidemie die in 2013 begon. De mazelen kwam voor in gebieden waar mensen zich om religieuze redenen vaak niet laten vaccineren.
Er zijn geen gevallen van polio gemeld. Vorig jaar waren de controles op polio geïntensiveerd in regio's in Nederland waar vluchtelingen worden opgevangen. Dit betrof vluchtelingen uit enkele niet-Europese landen waar het aantal poliogevallen was gestegen, zoals Syrië. Aangezien polio in die landen in 2014 minder voorkwam zijn de controles tot een normaal niveau teruggebracht.

### Ontwikkelingen voor toekomstige RVP-kandidaten

De Gezondheidsraad kan de minister adviseren om het aantal ziekten die onder het RVP vallen uit te breiden. Het RIVM houdt in de gaten hoe ziekten die hiervoor in aanmerking komen, zich ontwikkelen. In 2014 kwamen uitzonderlijk weinig infecties met het rotavirus voor. Ook daalde het aantal zieken door meningokokken serogroep B. Het aantal mensen met het waterpokken, gordelroos en hepatitis A is de afgelopen jaren stabiel gebleven.

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

# Synopsis

## The National Immunisation Programme in the Netherlands

*Surveillance and developments in 2014-2015*

In the Netherlands, participation in the National Immunisation Programme (NIP) is high, resulting in low incidences of most diseases included in the NIP. Yet coverage for vaccination against human papillomavirus (HPV) in girls is lower. Only a few severe adverse events following immunisation occurred. Reported adverse events are mostly mild and transient. Continuous monitoring of effectiveness and safety is necessary for the programme to remain optimal.

**Changes in the vaccination schedule in 2014-2015**
Since 2014, girls have been receiving a reduced number of doses against human papillomavirus (HPV). Two doses of HPV vaccine are offered to 12-year-old girls.

**Developments for diseases included in the NIP**
The switch to the 10-valent pneumococcal vaccine (PCV10) in 2011 reduced the number of invasive pneumococcal diseases caused by the additional PCV10 serotypes in the vaccinated age groups. A decrease in the incidence of IPD caused by the additional PCV10 serotypes was also seen in the adult age groups, which is probably due to indirect protection.
The incidence of pertussis increased in 2014 after a lower incidence in 2013, but was somewhat lower than during the epidemic year 2012. The incidence of mumps was low in 2014, but a resurgence of mumps and an endemic transmission were encountered in the first few months of 2015. The majority of the measles cases reported in 2014 belonged to the measles epidemic in the Bible Belt, which started in 2013.
No cases of polio were reported. The environmental routine surveillance, which was intensified in the region where refugees were first cared for in 2013, was changed to routine level again in April 2015.

**Developments for future NIP candidates**
The Health Council could advise the Dutch Minister of Health, Welfare and Sports on expansion of the NIP. The National Institute for Public Health and the Environment in the Netherlands (RIVM) investigates developments in potential future NIP candidates.
In 2014, the rotavirus season was exceptionally low. A decrease in meningococcal serogroup B disease was seen in 2014. Incidences of varicella zoster virus and hepatitis A remained stable over the previous years.

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

# Dutch National Immunisation Programme (NIP)

The RIVM continuously monitors the effectiveness and safety of the NIP in order to keep the programme optimal.

## Introduction of target disease into the NIP

- 1957 **Diphtheria (D)**
- **Pertussis (Pe)**
- **Tetanus (T)**
- **Polio (Po)**
- 1974 **Rubella (R)**
- 1976 **Measles (Me)**
- 1987 **Mumps (Mu)**
- 1993 ***Haemophilus infuenzae* type b (Hib)**
- 2002 **Meningococcal C (MenC) disease**
- 2006 **Pneumococcal (Pneu) disease**
- 2009 **Human papillomavirus (HPV)**
- 2011 **Hepatitis B (HepB)**

## Highlights in the NIP surveillance

### Area 1 - Surveillance of vaccination uptake

National vaccination coverage data

**2014 - 2015**

- > 94% of newborns is vaccinated
- Uptake for MMR-2 is below the WHO-target of 95%
- Uptake for HPV (2 doses) increased to 61%

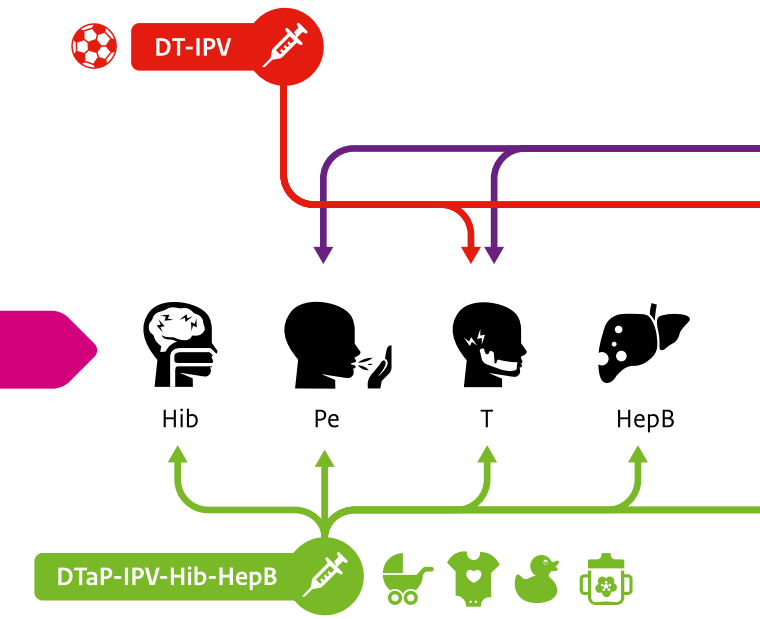
### Area 2 - Surveillance of adverse events

Enhanced spontaneous reporting of adverse events following immunisation

**2014 - 2015**

- Decreased number of reported adverse events

## Vaccinations




6-9 weeks · 3 months · 4 months · 11 months · 14 months · 4 years · 9 years · 12 years (girls only)

## Area 3 - Disease surveillance

Notifications by law, mortality, hospital admissions and general practitioner consultations

**2014 - 2015**

- Disease burden highest for invasive pneumococcal disease (IPD)
- Reduced number of IPD after introduction of 10-valent PCV
- Increased pertussis incidence

## Area 4 - Pathogen surveillance

Laboratory data

**2014 - 2015**

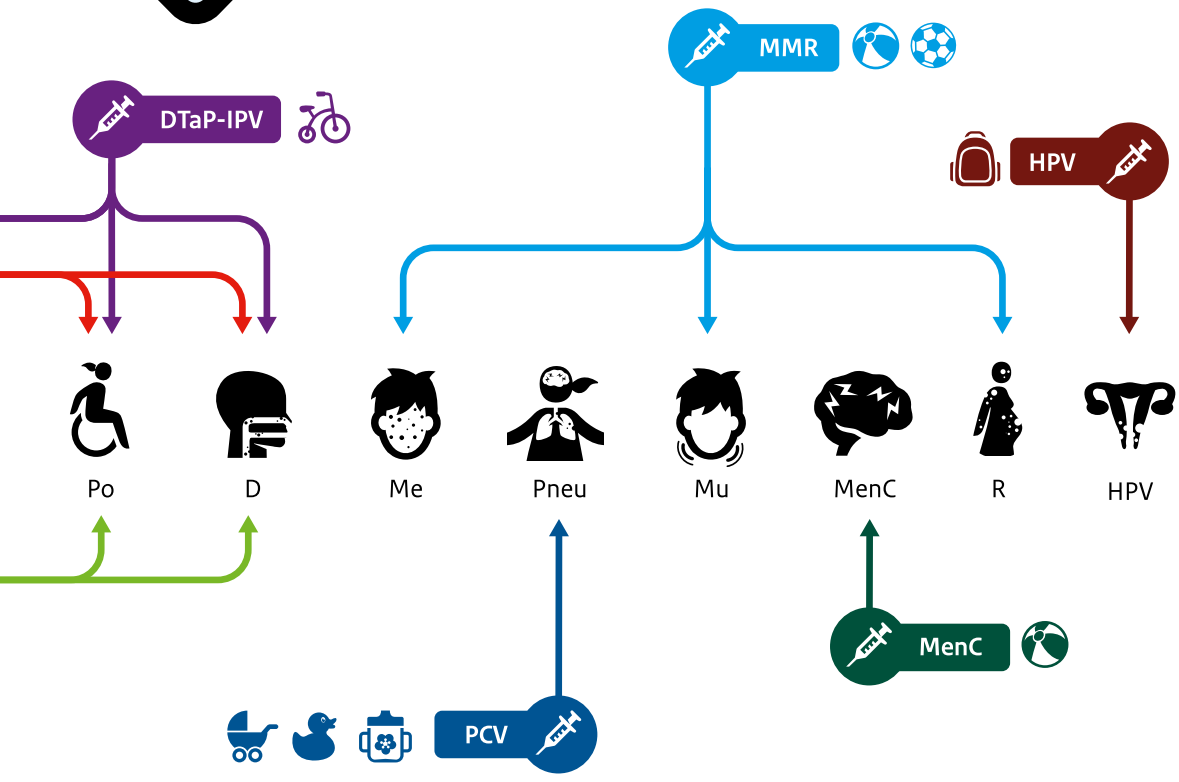
- Increase in circulating pertactin-deficient pertussis strains

## Area 5 - Immunosurveillance

Seroprevalence data from a representative sample

**2014 - 2015**

- People vaccinated against diphtheria remain protected for long time
- The design of a new seroprevalence survey (Pienter3) got approvement of the medical ethical committee



# Preface

This report presents an overview of the surveillance and developments in 2014-2015 with respect to the diseases included in the current National Immunisation Programme (NIP): diphtheria, pertussis, tetanus, poliomyelitis, *Haemophilus influenza*e serotype b (Hib) disease, mumps, measles, rubella, meningococcal serogroup C disease, hepatitis B, pneumococcal disease and human papillomavirus (HPV) infection. It also describes surveillance data concerning potential target diseases for which a vaccine is available: 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.

Some changes were made in the structure of the report following an evaluation of last year's report. The report is now structured as follows: Chapter 1 gives a short introduction. Recent results on vaccination coverage are discussed in Chapter 2 and the burden of diseases included in the NIP is the focus of Chapter 3. Public acceptance of vaccination and the communication of the NIP and adverse events following immunisation (AEFI) are described in Chapter 4 and Chapter 5, respectively. Chapter 6 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, the pathogen, the results of current and ongoing studies and international developments. Chapter 7 describes potential new target diseases that are under consideration for inclusion in the future NIP. Finally, in Chapter 8 an overview is given of vaccines for infectious diseases that 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 taken from various data sources for 1997 onwards are reported. Appendix 3 gives an overview of changes in the NIP since 2000 and Appendix 4 presents the composition of vaccines used in 2014-2015. Appendix 5 provides an overview of relevant websites.

# Comprehensive 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 and scientific developments are presented with regard to potential future 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)).

## Current vaccination schedule

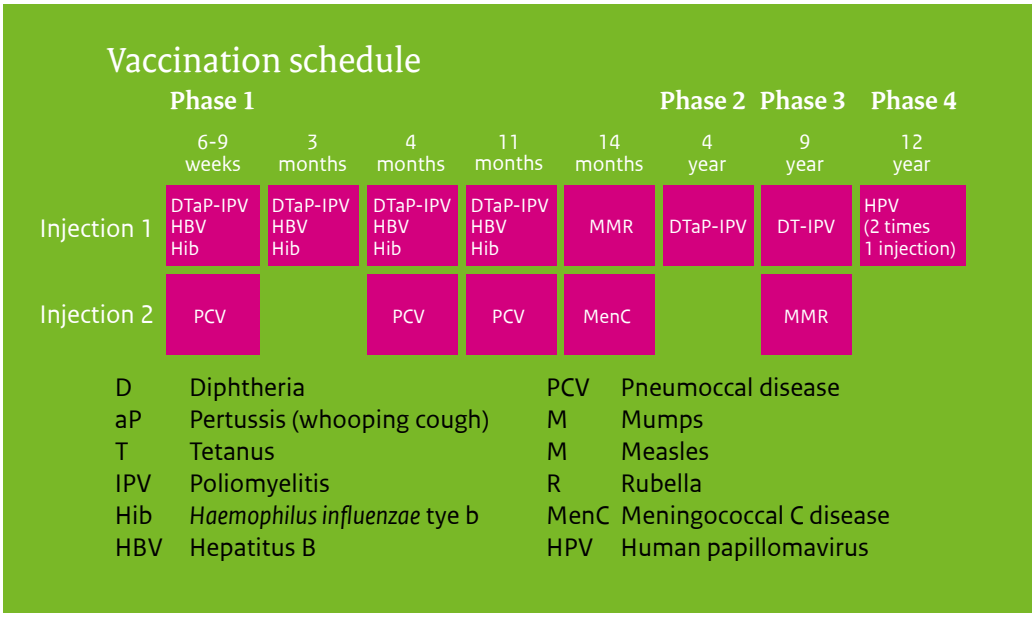



**Figure 1** Vaccination schedule of the NIP from 2014 onwards

### *Changes in vaccination schedule*

Since January 2014, adolescent girls are being vaccinated against HPV using a two-dose schedule (0, 6 months); up to that time a three-dose schedule had been recommended (0, 1, 6 months).

## Vaccination coverage

Vaccination coverage in the Netherlands is high. For HPV vaccination, the participation continued to increase compared with the previous report year. The uptake of the second MMR vaccination does not reach the target of 95% set by the World Health Organization (WHO).

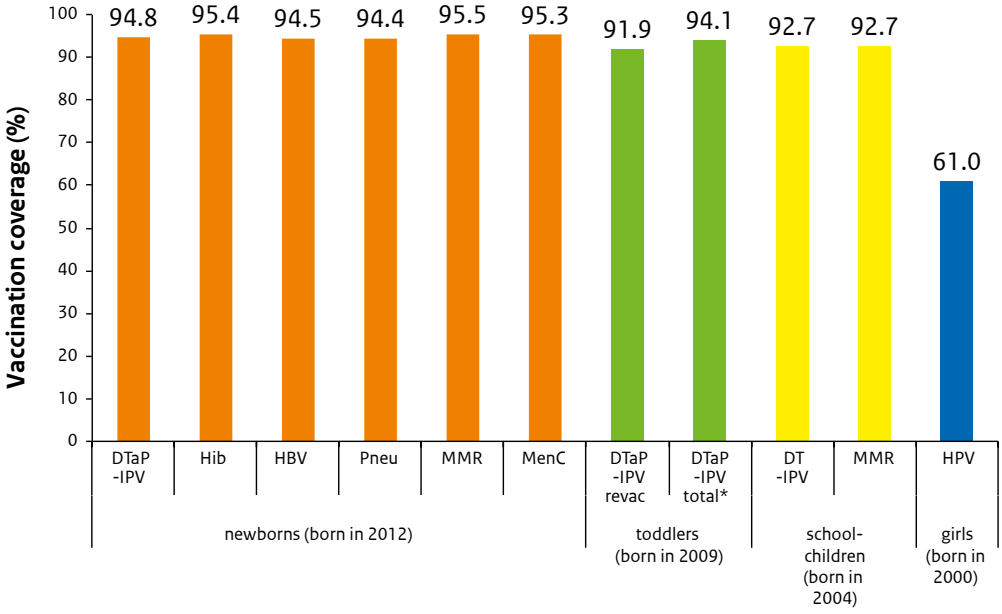



**Figure 2** Vaccination coverage per vaccine for age cohorts of newborns, toddlers, schoolchildren and adolescent girls in 2015

*DTaP-IPV total = Sum of DTaP-IPV revaccinated and base-immune at 2-5 years (not eligible for revaccination)

## Burden of Disease

National burden of disease estimates are expressed in Disability Adjusted Life Years (DALYs), which consists of the years lived with a disability (YLD) and the years of life lost (YLL) due to the disease or infection. The highest burden was estimated for invasive pneumococcal disease, followed by pertussis, measles and rotavirus infection.

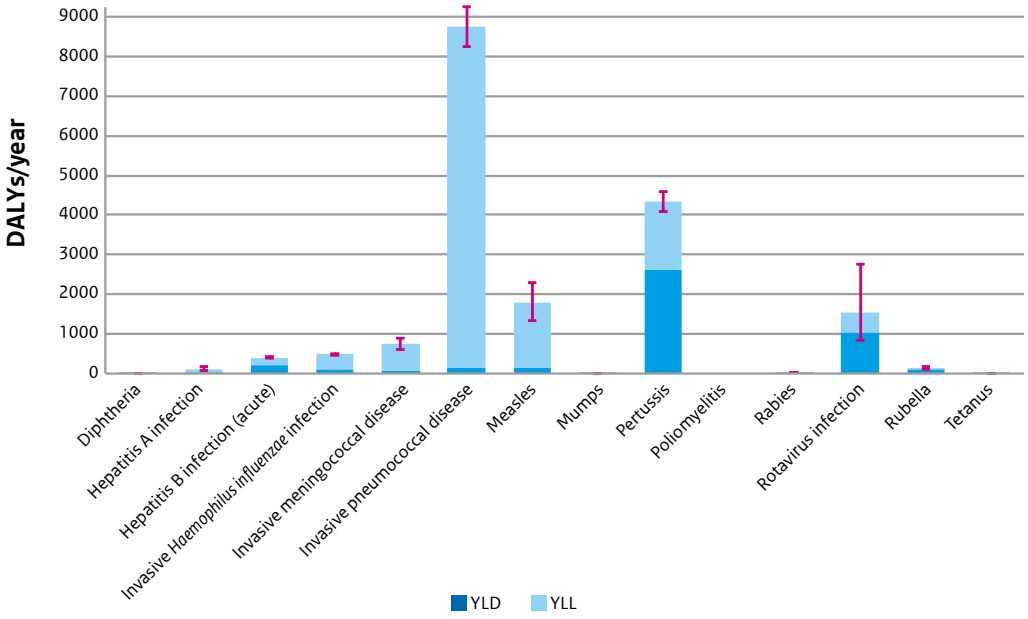



**Figure 3** Estimated average annual burden for new cases in the period 2010-2014, with the Years Lived with Disability (YLD) and Years of Life Lost (YLL) components shown separately

Note 1: red lines indicate 95% uncertainty intervals.
Note 2: for the three invasive diseases there was only a vaccine available against certain serotypes in the period 2010-2014: *Haemophilus influenzae* serotype **b (Hib)**, meningococcal **C** and pneumococcal serotypes **4, 6B, 9V, 14, 18C, 19F, 23F** and, from 2011 onwards, also serotypes **1, 5, 7F.**

## Acceptance of vaccination and communication

In the coming years the acceptance of vaccination among parents and child vaccine providers will be monitored using a recently developed system consisting of: a) focus groups containing members of the public and professionals, b) questionnaires at a certain time interval focused on the public and professionals, c) Child Welfare Centres as a sentinel, and d) monitoring online (social) media.
Vaccines not included in the public vaccination programme are underused at present.
To improve vaccination care, RIVM has started to conduct research on the perception of those vaccines not included in a public vaccination programme. The aim is to develop communication materials for the public and professionals. These materials may support the making of a well-considered decision on whether to vaccinate or not.
Behavioural inoculation seemed not to be an effective strategy to induce resistance to myths concerning the topic of HPV vaccination.

## Adverse events

In 2014, Lareb received 982 reports concerning a total of 1,950 adverse events following immunisation (AEFI), which is a decrease of almost 20% compared with 2013. The spectrum of reported AEFI is mostly in line with past years. No signals emerged indicating that vaccines used in the NIP would be unsafe.

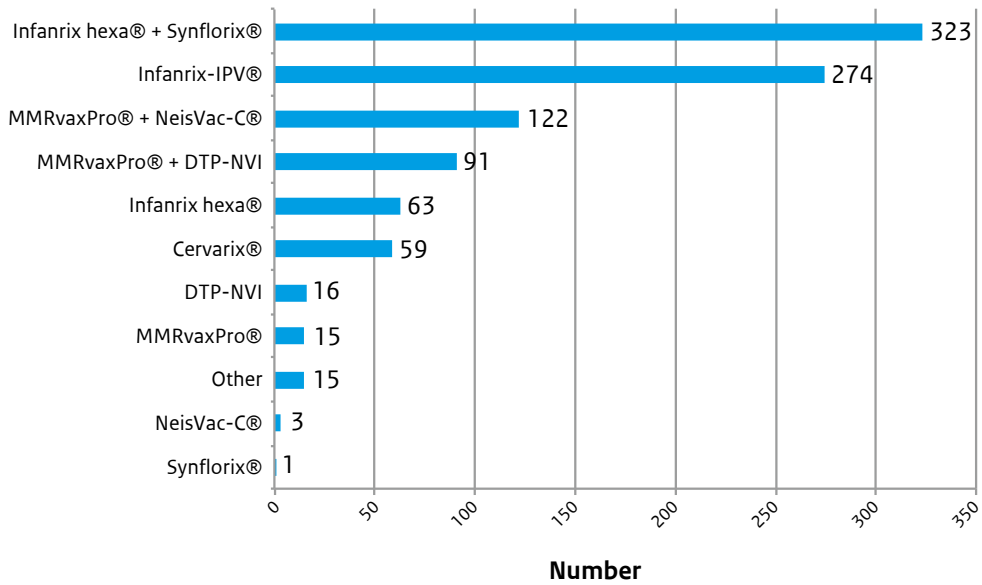



**Figure 4** Number of reports of adverse events (n=982) per suspected vaccine(s) in 2014

Source: Lareb

## Current NIP

### *Diphtheria*

In 2014 one diphtheria case was notified. In 2015, up to week 22, one diphtheria notification was also reported. Both patients contracted the disease abroad. One case received more than 3 vaccinations against diphtheria; the date of the last dose was unknown. In total, 12 Corynebacterium strains were tested on diphtheria-toxin using PCR and Elek-test. Two strains tested positive. In a large seroprevalence study performed in 2006-2007, the general population, eligible for NIP-vaccination, had high and long-lasting seroprotection. People born before NIP-introduction or adhering to an orthodox reformed religion had the highest susceptibility to diphtheria.

### *Pertussis*

The incidence of pertussis shows a biannual pattern, with epidemic peaks every two-years in both notifications and hospital admissions. The incidence based on notifications increased to 55 per 100,000 in 2014, following a lower incidence in 2013. In 2012, the incidence based on notifications was the highest since 1976 (83 per 100,000). In 2014, 2 deaths due to pertussis were registered.

The vaccine effectiveness (VE) of the primary series with the acellular pertussis vaccine, calculated using the screening method, is high until the age of 4 years. At this age, a booster dose is given. The VE of this booster dose decreases after 4-5 years.

During recent years, we observed an increase in Pertactin (Prn)-deficient strains circulating in the Netherlands. This is in line with findings in other countries and is probably related to the use of acellular vaccines. In a mouse model, VE was lower when mice, vaccinated with acellular pertussis, were challenged with Prn-deficient strains. Studies to assess the VE of three and five component acellular vaccines in a mouse model are planned.

Vaccination during pregnancy has been implemented in the UK, Belgium (Flanders) and several other countries. High effectiveness (91-93%) and a good safety profile were observed. Interference of maternal antibodies with the infant's immune response after vaccination was observed after the primary series, but restored after a booster dose. A survey showed that the intention to accept maternal pertussis vaccination in the Netherlands is about 60%.

### *Tetanus*

In 2014, no tetanus cases were notified. In 2015, up to week 24, one unvaccinated young adult was reported with tetanus. A Dutch study to assess the added value of a Tetanus Quick Stick (TQS), a bedside test for tetanus immunity, showed over-immunisation if the current practice of tetanus post-exposure prophylaxis (T-PEP) is followed. However, people born before the introduction of the tetanus vaccination were not always eligible for T-PEP according to the current guideline, but had a negative TQS, probably indicating non-protection.

### *Poliomyelitis*

In the Netherlands, no cases of poliomyelitis were reported in 2014 and 2015 until week 24. In January 2015, a Sabin type 1 oral polio vaccine (OPV) strain was found once in a sewage sample at the point where refugees and asylum seekers receive first care after entry. Through routine enterovirus-surveillance, a VDPV type 3 was found in a young Syrian refugee in July 2015. Follow up of the case and surrounding contacts revealed no circulation of the poliovirus. Great progress has been made in the worldwide efforts to eradicate polio. After eradication, vaccination remains necessary, preferably with the inactivated polio vaccine (IPV) instead of OPV. Furthermore, the World Health Organization (WHO) adopted a plan to minimize poliovirus facility-associated risks.

### *Haemophilus influenzae type b (Hib) disease*

The total number of cases of invasive disease caused by *Haemophilus influenzae* serotype b (Hib) in 2014 (n=29) was the same as previous year. The incidence among 0-4 year-olds decreased from 1.43 per 100,000 (n=13) in 2013 to 0.89 per 100,000 in 2014 (n=8), whereas in the other age-groups, except for 65 years and older, the incidence increased slightly. Since 2006 (n=14) the number of vaccine failures for invasive Hib disease decreased to an average of 7 vaccine failures per year with a range of 4 to 9 vaccine failures per year. Since 2004, there has been a steady increase in the number of cases caused by nontypeable Hi strains (NTHi) (71 in 2004 to 117 in 2014).

### *Mumps*

The number of mumps notifications was low in 2014 (n=40). It increased in the first 5 months of 2015 and new molecular methods suggest the endemic transmission of mumps in this period. The mumps virus genotype that causes most of the mumps cases in the Netherlands is genotype G.

### *Measles*

In 2014, 140 cases of measles were reported, the majority of which belonged to the epidemic in areas with low vaccination coverage ('Bible Belt') in the Netherlands that lasted from May 2013 to March 2014, in which a total of 2,700 cases were reported. Later in 2014, some small clusters occurred that were import related. A 17-year-old patient died of subacute sclerosing panencephalitis (SSPE), a late complication of a measles infection at 4 years of age. Many research projects related to the 2013-2014 epidemic are still ongoing.

### *Rubella*

In 2014 and in 2015 up to week 25, only two cases of rubella were reported. A national guideline on rubella screening during pregnancy is being developed and is expected in 2015/2016.

### *Meningococcal serogroup C (MenC) disease*

In 2014, 3 cases and in 2015 (until June) 5 cases of MenC disease were reported, including one vaccine failure. This is the fourth vaccine failure case to occur since the introduction of the conjugated MenC vaccine in 2002.

### *Hepatitis B*

In 2014, the incidence of acute hepatitis B virus infections (HBV) notifications decreased slightly and remained low at 0.8 cases per 100,000 people. For acute cases, sexual contact was the most common reported transmission route. Similar to previous years, genotype A was the most common genotype among acute cases in 2014. A platform to combine molecular data with epidemiological and transmission data is being developed to facilitate the efficient surveillance of HBV and the detection of antiviral resistance and immune escape variants.

### *Pneumococcal disease*

Introduction of 7-valent pneumococcal conjugate vaccine (PCV7) in 2006 decreased 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 2013-2015. The switch to 10-valent pneumococcal conjugate vaccine (PCV10) in 2011 reduced the number of IPD cases caused by the additional PCV10 serotypes (1, 5 and 7F) in the vaccine-eligible age groups. A decrease in the incidence of IPD caused by the additional PCV10 serotypes in the adult age groups was seen in 2013-2015. This is probably due to herd protection as a result of PCV10 introduction for children. However, longer follow-up is needed to establish this since natural fluctuations over time cannot be ruled out yet. The incidence of non-vaccine-type IPD increased after the introduction of PCV7. The increase in 2013-2015 was very small.

### *Human papillomavirus (HPV)*

Incidences of HPV-associated cancers and deaths have slightly increased over the last decade in the Netherlands. The VE of the bivalent vaccine against incident and persistent infections in a cohort study is high up to four years post-vaccination. Persistent HPV16/18 infections were found to have significantly higher baseline viral loads than clearing infections. Antibody avidity after a two-dose schedule (0, 6 months) showed no remarkable differences with a three-dose schedule, indicating the similar quality of the antibody response.

## Future NIP candidates

### *Rotavirus*

The incidence of rotavirus-associated gastroenteritis seen in the Netherlands was exceptionally low in 2014. In total, 607 diagnoses were reported by the Working Group Clinical Virology in 2014. The number of diagnoses in 2015 was in line with the 2012 season, which had been a low season. Genotype G9P[8] was most commonly found in the Netherlands in 2014. The relative prevalence of G2P[4] shows a slight but steady increase since 2011.

*Varicella zoster virus (VZV) infection*
The VZV epidemiology (varicella and herpes zoster) is comparable to previous years. The incidence based on GP consultations in 2013 amounted to 280 per 100,000 for varicella and 510 per 100,000 for herpes zoster. The cost-effectiveness of varicella vaccination is strongly affected by its impact on herpes zoster and the time horizon for economic assessment: in the absence of exogenous immune boosting, varicella vaccination with high coverage is expected to be cost-effective and may even be cost-saving, while it is not expected to be cost-effective on reasonable time scales if immune boosting is present.

*Hepatitis A*
In 2014, the incidence of reported hepatitis A infections (0.6 cases per 100,000) remained low, as in recent years. More than half of the 105 cases were younger than 20 years and clusters occurred almost only amongst these cases. Fifty-three per cent of the Dutch cases were reported to be travel-related, almost half of them in Morocco.

*Meningococcal serogroup B (MenB) disease*
In 2014, a decrease in MenB disease was seen (60 cases in 2014 (0.36 per 100,000), compared with 88 in 2013 (0.52 per 100,000), which was mostly due to a decrease among 0-4 year-olds and 40-64 year-olds, while among 5-9 year-olds the incidence increased slightly.

*Meningococcal non-B and non-C disease*
In 2014, 19 (23%) meningococcal cases were caused by non-serogroup B or C types from a total of 83 cases.

## Dutch Caribbean

The participation among infants from the Caribbean Netherlands for the DTaP-IPV, MMR and pneumococcal vaccination is high. In 2014, the Department for Vaccine Supply and Prevention Programmes (DVP/RIVM) prepared for the vaccine distribution and delivery to the Dutch Caribbean municipalities, Bonaire, St Eustatius and Saba (BES).
HPV immunisation will be introduced on Bonaire from September 2015 onwards.

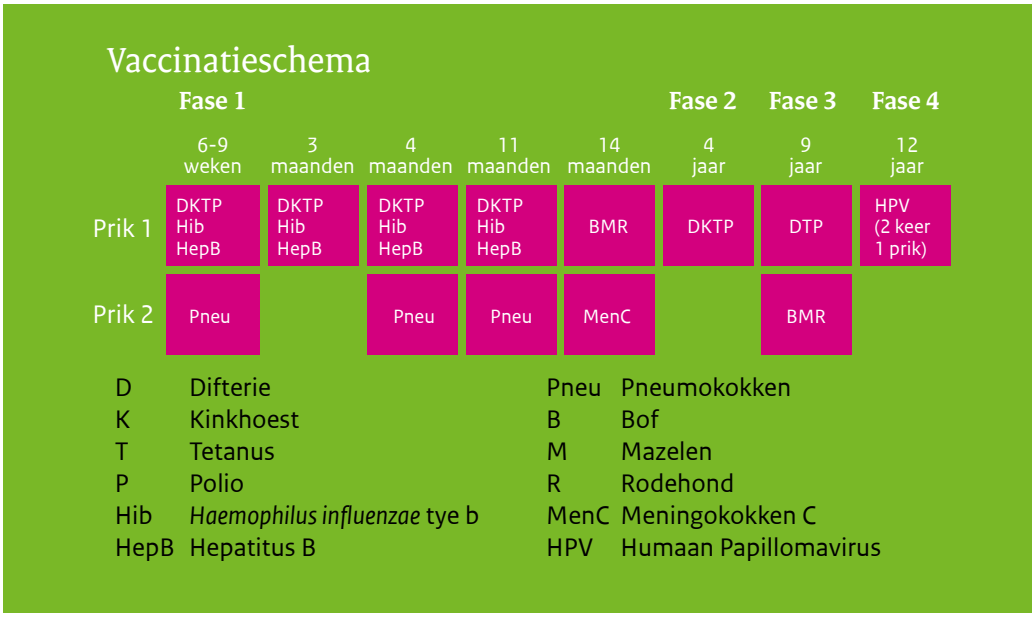
## General conclusion

Continuous monitoring of both current and potential future target diseases is necessary to optimize the prevention of these diseases by maintaining or adapting the programme.

# Uitgebreide samenvatting

In dit rapport worden surveillance data en wetenschappelijke ontwikkelingen in Nederland gepresenteerd voor ziekten waartegen binnen het Rijksvaccinatieprogramma (RVP) gevaccineerd wordt (difterie, kinkhoest, tetanus, polio, *Haemophilus influenzae* serotype b (Hib), mazelen, bof, rodehond, meningokokken serogroep C (MenC), hepatitis B, pneumokokkenziekte en humaan papillomavirus (HPV)). Ook worden surveillance data en wetenschappelijke ontwikkelingen beschreven voor ziekten waarvoor het beschikbare vaccin (nog) niet is opgenomen in het RVP (rotavirus, varicella zoster-virus (VZV), hepatitis A, meningokokken serogroep B (MenB) en andere meningokokken serogroepen (n.l. Y, W, A, X, Z, 29E).

## Huidig vaccinatieschema



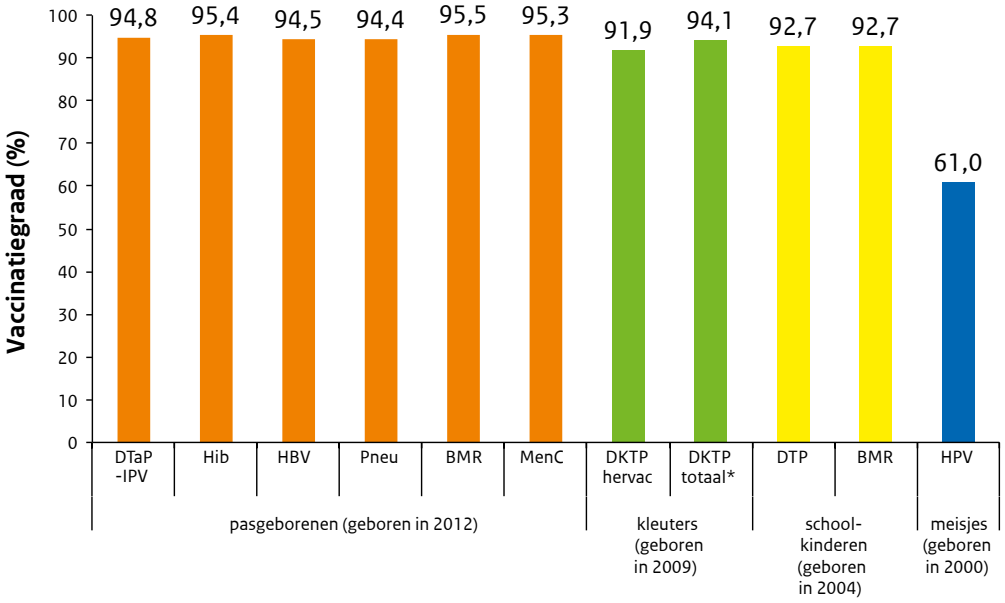

**Figuur 1** Vaccinatieschema van het RVP vanaf 2014

### *Wijzigingen in het vaccinatieschema*

Sinds januari 2014 worden meisjes in het jaar dat ze 13 worden gevaccineerd tegen HPV in een twee-doses schema (0, 6 maanden). Voorheen gebeurde dit middels een drie-doses schema (0, 1, 6 maanden).

## Vaccinatiegraad

De vaccinatiegraad in Nederland is hoog. Voor HPV-vaccinatie is de vaccinatiegraad verder gestegen ten opzichte van het vorige rapportage jaar. De opkomst voor de tweede BMR vaccinatie bereikt niet de 95% die de World Health Organization (WHO) als doel heeft gesteld.

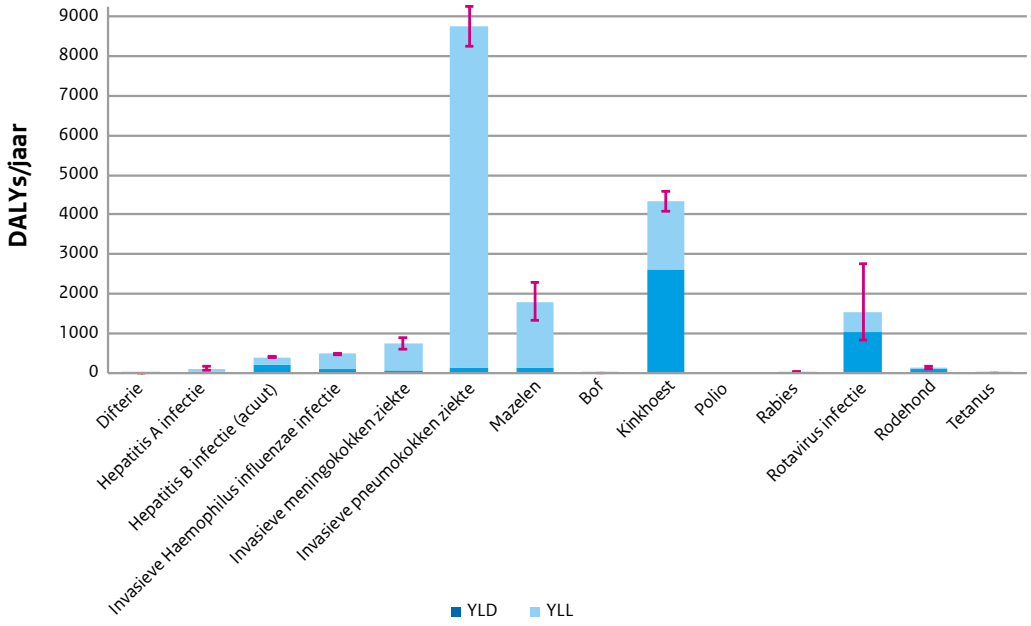



**Figuur 2** Vaccinatiegraad per vaccin voor pasgeborenen, kleuters, schoolkinderen en adolescente meisjes in 2015

* DKTP totaal = som gerevaccineerd (DKTP revac) + basisimmuun 2-5 jaar (komen niet in aanmerking voor revaccinatie).

## Ziektelast

De schattingen van de ziektelast in Nederland worden uitgedrukt in Disability Adjusted Life Years (DALY's), die bestaat uit het aantal jaren geleefd met ziekte (YLD) en het aantal verloren levensjaren (YLL) door de ziekte of infectie. De hoogste ziektelast is geschat voor invasieve pneumokokkenziekte gevolgd door kinkhoest, mazelen en rotavirusinfectie.




**Figuur 3** Geschatte jaarlijkse ziektelast voor nieuwe cases in de periode 2010-2014, met jaren geleefd met ziekte (YLD) en verloren levensjaren (YLL) apart gepresenteerd

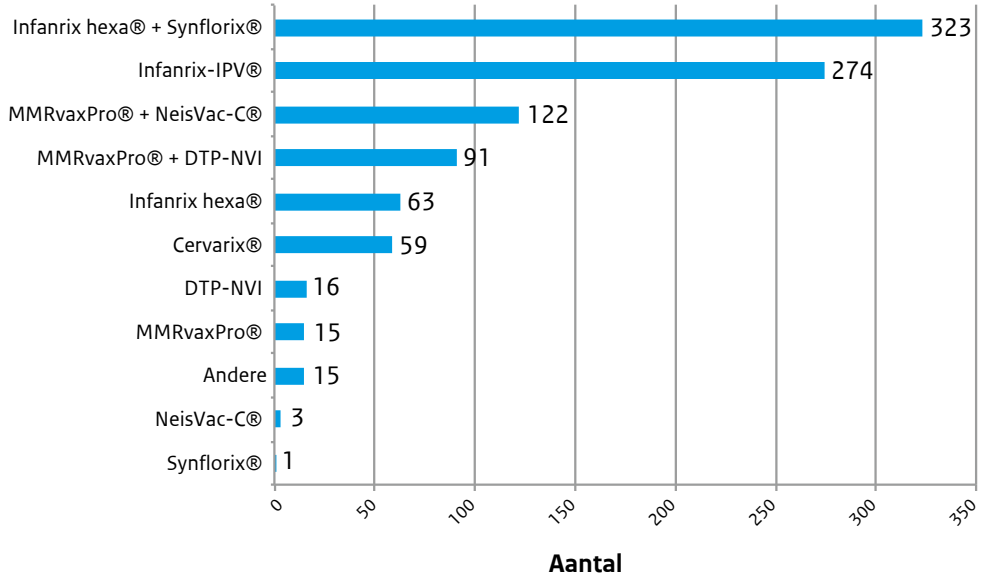
ad 1: de rode lijnen geven het 95% betrouwbaarheidsinterval weer
ad 2: voor de invasieve ziekten was alleen een vaccin beschikbaar tegen bepaalde serotypen in de periode 2010-2014: *Haemophilus influenzae* serotype **b (Hib)**, meningokokken **C** en pneumokokken serotype **4, 6B, 9V, 14, 18C, 19F, 23F** en vanaf 2011 ook serotype **1, 5, 7F**.

## Acceptatie van vaccinatie en communicatie

In de komende jaren zal de acceptatie van vaccinatie onder ouders en professionals worden gemonitord met behulp van een recent ontwikkeld systeem. Het systeem bestaat uit: a) focusgroepen bestaande uit burgers en professionals, b) vragenlijsten met een bepaalde tijdsinterval voor burgers en professionals, c) consultatiebureaus en d) monitoring van online (sociale) media.
Het RIVM is gestart met onderzoek naar de beleving rondom vaccins die niet in een RVP zijn opgenomen. Het doel is communicatiemateriaal te ontwikkelen voor het publiek en professionals zodat ouders een weloverwogen beslissing kunnen nemen om hun kind al dan niet te laten vaccineren. Gedragsinenting leek geen effectieve strategie om weerstand te induceren tegen mythes over HPV-vaccinatie.

## Bijwerkingen

In 2014 ontving Bijwerkingencentrum Lareb 982 meldingen met 1950 mogelijke bijwerkingen van vaccins. Dit is een daling van het aantal meldingen van bijna 20% ten opzichte van 2013. De aard van de gemelde bijwerkingen is vergelijkbaar met de vorige jaren. De meldingen van vermoede bijwerkingen in 2014 geven geen aanleiding tot verontrustende signaleringen.




**Figuur 4** Aantal meldingen van bijwerkingen (aantal = 982) per vaccin in 2014

Bron: Lareb

## Huidig RVP

*Difterie*

In 2014 was er 1 melding van difterie. Ook in de eerste 22 weken van 2015 is er één geval van difterie gemeld. Beide patiënten hebben de ziekte opgelopen in het buitenland. Eén van de patiënten was drie keer gevaccineerd, de datum van de laatste dosis is onbekend. In totaal zijn er in deze periode 12 Corynebacterium stammen onderzocht op toxigeniciteit. Twee stammen werden positief bevonden. In PIENTER 2, een grote seroprevalentiestudie uitgevoerd in 2006-2007, is voor de algemene bevolking die in aanmerking kwam voor het RVP, een goede, langdurige bescherming tegen difterie aangetoond. Mensen die zijn geboren vòòr invoering van het RVP en streng orthodox-gereformeerde mensen lopen meer risico om difterie te krijgen.

*Kinkhoest*

De incidentie van kinkhoest laat tweejaarlijkse pieken zien in meldingen en ziekenhuis-opnames. De incidentie van kinkhoestmeldingen was in 2014 gestegen naar 55 per 100.000 na een lagere incidentie in 2013. In 2012 was de incidentie van meldingen met 83 per 100.000 het hoogst sinds 1976. In 2014 werden 2 overlijdens door kinkhoest geregistreerd.
Na de invoering van een acellulair kinkhoest combinatievaccin in 2005, is de vaccineffectiviteit (VE) van de primaire serie, tot aan de leeftijd van 4 jaar, hoog. De VE van de herhalings-vaccinatie op 4 jaar neemt 4-5 jaar na deze booster af.
De laatste jaren zien we in Nederland en andere landen een toename van het percentage Pertactine (Prn)-deficiënte stammen. Waarschijnlijk houdt dit verband met de introductie van acellulaire vaccins. In proeven met muizen die gevaccineerd waren met een acellulair vaccin, was de VE lager als de muis werd geïnfecteerd met een Prn-deficiënte stam. Aanvullende proeven om de VE van acellulaire vaccins met een verschillend aantal componenten met elkaar te vergelijken zijn in voorbereiding.
Vaccinatie tijdens de zwangerschap is al ingevoerd in Engeland, Vlaanderen en diverse andere landen. Een hoge effectiviteit (91-93%) en een goede veiligheid werden geobserveerd. Studies hebben laten zien dat maternale antistoffen het immuunrespons van het kind verstoren na de primaire serie. Dit lijkt zich echter na de boostervaccinatie te herstellen. Onderzoek toont aan dat de acceptatie van kinkhoestvaccinatie tijdens de zwangerschap in Nederland ongeveer 60% bedraagt.

*Tetanus*

In 2014 zijn er geen meldingen van tetanus gedaan. In de eerste 24 weken van 2015 is er 1 geval van tetanus gemeld. Het betrof een ongevaccineerde jongvolwassene. Een Nederlands onderzoek naar de eventuele meerwaarde van de tetanus Quick Stick (TQS), een sneltest om antistoffen tegen tetanustoxoid aan te tonen, laat zien dat er bij de huidige praktijk van tetanus-post expositie profylaxe (T-PEP) vaak sprake is van overbehandeling. Mensen die zijn geboren vòòr invoering van tetanusvaccinatie in het RVP, krijgen echter vaak geen T-PEP, terwijl ze waarschijnlijk niet beschermd zijn.

### *Polio*

In Nederland zijn er in 2014 en in 2015 tot week 24 geen gevallen van poliomyelitis gemeld. Wel is er in januari 2015 éénmalig een Sabin oraal polio vaccin (OPV) 1 vaccin stam gevonden via de rioolwatersurveillance van ter Apel, de eerste opvangplaats van asielzoekers.
Er is grote vooruitgang geboekt bij de wereldwijde eradicatie van polio. Ook na eradicatie zal er gevaccineerd moeten worden tegen polio. Hierbij wordt aanbevolen om OPV te vervangen door geïnactiveerd polio vaccin (IPV). De World Health Organization (WHO) heeft een plan opgesteld om de aanwezigheid en het gebruik van poliovirussen in laboratoria en andere instituten in kaart te brengen om de risico's op uitbraken via deze route te minimaliseren.

### *Haemophilus influenzae type b (Hib) ziekte*

Het totaal aantal invasieve ziekten veroorzaakt door *Haemophilus influenzae* serotype b (Hib) in 2014 (aantal=29) was gelijk aan in het jaar daarvoor. De incidentie in 0-4-jarigen is gedaald van 1,43 per 100.000 in 2013 naar 0,89 per 100.000 in 2014. In de overige leeftijdsgroepen, met uitzondering van 65-jarigen en ouder, is de incidentie licht gestegen. Sinds 2006 is het aantal vaccinfalen (aantal=14) van invasieve Hib-ziekten gedaald tot gemiddeld 7 per jaar met een range van 4 tot 9 vaccinfalen per jaar. Sinds 2004 is een constante stijging te zien in het aantal ziektegevallen veroorzaakt door een niet-typeerbare Hi stam (71 in 2004 tot 117 in 2014).

### *Bof*

Het aantal gevallen van bof was laag in 2014 (40). In de eerste vijf maanden van 2015 is de incidentie toegenomen. Nieuwe moleculaire onderzoeksmethoden toonde endemische transmissie aan. Bofinfecties worden in Nederland voornamelijk veroorzaakt door bof virus genotype G.

### *Mazelen*

In 2014 werden 140 gevallen van mazelen gemeld, waarvan de meesten behoorden tot de epidemie in de 'bible belt' die tussen mei 2013 en maart 2014 plaatsvond. Tijdens deze epidemie werden in totaal 2700 gevallen van mazelen gemeld. Later in 2014 werden enkele kleine import gerelateerde clusters gezien. Een 17-jarige patiënt is overleden aan subacute scleroserende panencefalitis (SSPE), een late complicatie van een mazeleninfectie op 4-jarige leeftijd. Er lopen nog diverse onderzoeksprojecten gerelateerd aan de mazelen epidemie in 2013-2014.

### *Rodehond*

In 2014 en 2015 tot week 25 werden twee gevallen van rodehond gemeld. Een landelijke richtlijn over rubellascreening tijdens de zwangerschap is in ontwikkeling en wordt verwacht in 2015/2016.

### *Meningokokken serogroep C (MenC)-ziekte*

In 2014 werden 3 gevallen van MenC-ziekte gerapporteerd. In 2015 (tot juni) waren dit er 5, inclusief 1 geval van vaccinfalen. Dit is het vierde geval van vaccinfalen sinds de introductie van het geconjugeerd MenC-vaccin in 2002.

*Hepatitis B*

In 2014 is de incidentie van acute hepatitis B-virusinfectie (HBV) iets verder afgenomen en blijft laag met 0,8 gevallen per 100.000 inwoners. Onder acute gevallen is seksueel contact de meest gerapporteerde transmissieroute. Vergelijkbaar met eerdere jaren is genotype A het meest voorkomende bij acute HBV-infectie. Om de surveillance van HBV en de detectie van antivirale resistentie en immuun-escape varianten te faciliteren wordt gewerkt aan een platform waarbinnen moleculaire en epidemiologische gegevens gecombineerd kunnen worden.

*Pneumokokkenziekte*

Introductie van het 7-valente pneumokokkenvaccin (PCV7) in 2006 heeft geleid tot een daling in vaccin-type invasieve pneumokokkenziekten van 7,4 per 100.000 per jaar in 2004-2006 naar minder dan 1 per 100.000 per jaar in 2013-2015. Door de verandering naar het 10-valente pneumokokkenvaccin (PCV10) in 2011 is het aantal invasieve pneumokokkenziekten veroorzaakt door de additionele PCV10 serotypen (1, 5 en 7F) gedaald in de gevaccineerde leeftijdsgroepen. In 2013-2015 werd ook een daling in incidentie van invasieve pneumokokkenziekte veroorzaakt door de additionele PCV10 serotypen in volwassen leeftijdsgroepen gezien. Dit wordt waarschijnlijk veroorzaakt door kudde-immuniteit na introductie van PCV10 voor kinderen. Langere follow-up is echter noodzakelijk om natuurlijke fluctuaties uit te sluiten. De incidentie van invasieve pneumokokkenziekte veroorzaakt door niet-vaccintypen is gestegen na de introductie van PCV7. In 2013-2015 was deze stijging echter zeer klein.

*Humaan papillomavirus (HPV)*

In Nederland is in het laatste decennium de incidentie van HPV-geassocieerde kankers en sterfte licht gestegen. Uit de resultaten van een cohortstudie kwam een hoge VE van het bivalente vaccin tegen incidente en persistente infecties tot 4 jaar na vaccinatie. Persisterende HPV16/18 infecties hebben hogere virale loads dan klarende infecties. Er zijn geen opmerkelijke verschillen gevonden in antistof aviditeit na een twee-doses schema (0, 6 maanden) vergeleken met een drie-doses schema (0, 1, 6 maanden), wat een vergelijkbare kwaliteit van antistof respons suggereert.

## Toekomstige RVP kandidaten

*Rotavirus*

De geregistreerde incidentie van rotavirus-geassocieerde gastro-enteritis in Nederland was uitzonderlijk laag in 2014. In totaal werden in 607 rotavirusdiagnoses gerapporteerd door de Werkgroep Klinische Virologie. Het genotype G9P[8] werd in 2014 het meest gezien. Sinds 2011 is er een kleine, maar gestage toename van het voorkomen van G2P[4] zichtbaar.

*Varicella zoster virus (VZV) infectie*

De VZV-epidemiologie (waterpokken en gordelroos) is vergelijkbaar met voorgaande jaren. De incidentie gebaseerd op huisartsenbezoeken in 2013 was voor waterpokken 280 per 100.000 en voor gordelroos 510 per 100.000. De kosteneffectiviteit van waterpokkenvaccinatie wordt sterk beïnvloed door de impact op gordelroos en de tijdshorizon voor economische analyse: in afwezigheid van exogene immuunboosting wordt verwacht dat waterpokkenvaccinatie bij een hoge vaccinatiegraad kosteneffectief of zelfs kostenbesparend is, terwijl verwacht wordt dat vaccinatie niet binnen redelijke termijn kosteneffectief is als er wel sprake is van immuunboosting.

*Hepatitis A*

De incidentie van gerapporteerde hepatitis A-infecties bleef in 2014, evenals in de afgelopen jaren, laag (0,6 per 100.000). Meer dan de helft van de 105 patiënten was jonger dan 20 jaar en clusters ontstonden vrijwel alleen binnen deze groep patiënten. 53% van de hepatitis A-infecties waren in het buitenland opgelopen, waarvan bijna de helft in Marokko.

*Meningokokken serogroep B (MenB)-ziekte*

In 2014 is het aantal MenB-ziekten gedaald van 88 in 2013 (0,52 per 100.000) tot 60 in 2014 (0,36 per 100.000). Deze daling werd voornamelijk gezien in 0-4-jarigen en 40-64-jarigen. Onder 5-9-jarigen was een lichte stijging te zien.

*Meningokokken niet-B en niet-C ziekten*

In 2014 waren 19 (23%) van de in totaal 83 meningokokken gevallen veroorzaakt door een niet-B of -C serogroep.

## Nederlandse Cariben

De vaccinatiegraad voor DTaP-IPV-, BMR- en pneumokokkenvaccinatie onder zuigelingen in de Caribisch Nederland is hoog. In 2014 treft de Dienst Vaccinvoorziening en Preventieprogramma's (DVP) van het RIVM voorbereidingen voor de distributie en levering van vaccins aan de Nederlandse Caribische gemeenten Bonaire, St Eustatius en Saba (BES). HPV-vaccinatie wordt vanaf september 2015 geïntroduceerd op Bonaire.

## Algemene conclusie

Continue monitoring van zowel ziekten waartegen in het huidige RVP gevaccineerd wordt als potentiele toekomstige ziekten is nodig voor het optimaliseren van de preventie van deze ziekten door het behouden of aanpassen van het programma.

# 1
# Introduction

## 1.1 Vaccination schedule of the NIP

The 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, in addition to DTPIPV, 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). In the Netherlands, vaccinations within the NIP are administered to the target population free of charge and on a voluntary basis.

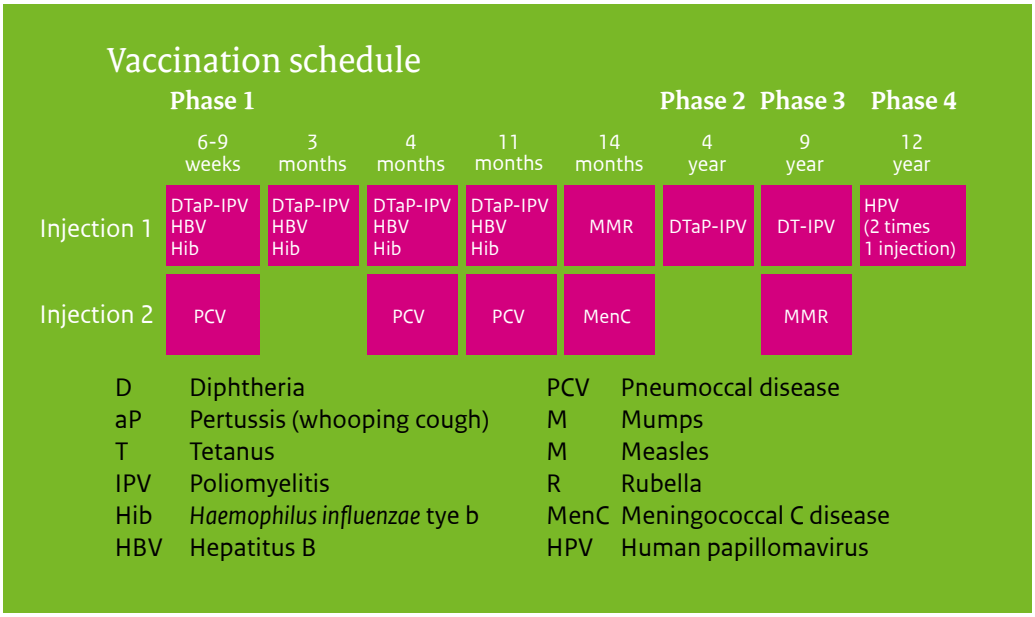



**Figure 1.1** Vaccination schedule of the National Immunisation Programme (NIP) from 2014 onwards.

Source: *http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/ Professionals*

### 1.1.1 Changes in vaccination schedule in 2014/2015

Since January 2014, vaccination against HPV for adolescent girls has been changed from a three-dose schedule (0, 1, 6 months) to a two-dose schedule (0, 6 months), following the licensing of the bivalent vaccine for a two-dose schedule. When started after the fifteenth birthday, three doses are still needed (0, 1, 6 months).

## 1.2 Dutch Caribbean

In 2014, the Department for Vaccine Supply and Prevention Programmes of the National Institute for Public Health and the Environment in the Netherlands (DVP/RIVM) prepared for vaccine distribution and delivery to the Dutch Caribbean municipalities, Bonaire, St Eustatius and Saba (BES). A quality control system has been set up, procedures have been tested and staff have been trained. A carrier has been selected, an audit carried out and some corrective measures have been taken so that by Q4 2015 vaccines from Dutch stock at RIVM will be transported following validated procedures.

HPV immunisation will be introduced on Bonaire from September 2015 onwards. This is the last adaptation to harmonise the immunisation programme in the Caribbean and European Netherlands.

## 1.3 Vaccination of risk groups

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 to those with an increased risk of morbidity and mortality following influenza. Vaccination against tuberculosis is offered to the 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.

## 1.4 Literature


1*. RIVM. Griepprik. Available from: *www.rivm.nl/griepprik/voor_wie/*.

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4*. Teirlinck CJPM, van Asten L, Brandsema PS, Dijkstra F, Euser SM, van Gageldonk-Lafeber AB, et al. Annual report surveillance respiratory infectious diseases 2013, the Netherlands. Bilthoven: RIVM, 2014 150002006.


* RIVM publication

# 2
# Vaccination coverage

*E.A. van Lier*

## 2.1 Key points

- Vaccination coverage in the Netherlands is high.
- For HPV vaccination, the participation continued to increase, compared with the previous report year, to 61%.
- The uptake of the second MMR vaccination does not reach the target of 95% set by the World Health Organization (WHO).

## 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 2015 (Table 2.1) [1]. The exception is the HPV vaccination against cervical cancer, for which the participation continued to increase compared with the previous report year (to 61%). The participation for the hepatitis B vaccination for children born in 2012, the first year in which all infants were eligible for the hepatitis B vaccination, is 94%. The participation among infants from the Caribbean Netherlands for the DTaP-IPV, MMR and pneumococcal vaccination is also high.

The participation for the MMR vaccination for 9-year-olds (93%) is identical to the participation for the DT-IPV vaccination this time; usually the participation for the MMR vaccination is slightly lower. This is an improvement, but the required participation has not yet been reached. A participation of at least 95% is important because of the aim of the WHO to eliminate measles worldwide. Such a high vaccination coverage is important to protect the general population against outbreaks (herd immunity).

To protect infants effectively against the diseases of the NIP, it is also important to give vaccinations on time. The proportion of infants that received the first DTaP-IPV vaccination on time, i.e. before they are 10 weeks old, increased further to 89%. In addition, the timely and full participation in the primary DTaP-IPV series (the first three vaccinations) improved from 60% for children born in 2007 to 69% for children born in 2012.

## 2.3 Tables and Figures

**Table 2.1** Vaccination coverage per vaccine for age cohorts of newborns, toddlers, schoolchildren and adolescent girls in 2006-2015

| | Newborns* | | | | | | |
|---|---|---|---|---|---|---|---|
| Report Year | cohort | DTaP -IPV | Hib | HBV [a] | Pneu ** | MMR | MenC |
| 2006 | 2003 | 94.3 | 95.4 | 15.2 | - | 95.4 | 94.8 |
| 2007 | 2004 | 94.0 | 95.0 | 17.1 | - | 95.9 | 95.6 |
| 2008 | 2005 | 94.5 | 95.1 | 17.9 | - | 96.0 | 95.9 |
| 2009 | 2006 | 95.2 | 95.9 | 18.6 | 94.4 | 96.2 | 96.0 |
| 2010 | 2007 | 95.0 | 95.6 | 19.3 | 94.4 | 96.2 | 96.1 |
| 2011 | 2008 | 95.4 | 96.0 | 19.4 | 94.8 | 95.9 | 95.9 |
| 2012 | 2009 | 95.4 | 96.0 | 19.5 | 94.8 | 95.9 | 95.9 |
| 2013 | 2010 | 95.5 | 96.1 | 19.7 | 95.1 | 96.1 | 96.0 |
| 2014 | 2011 | 95.4 | 95.9 | 51.4 | 95.0 | 96.0 | 95.8 |
| 2015 | 2012 | 94.8 | 95.4 | 94.5 | 94.4 | 95.5 | 95.3 |

| | Toddlers* | | | | Schoolchildren* | | | Adolescent girls* | |
|---|---|---|---|---|---|---|---|---|---|
| Report Year | cohort | DTaP -IPV [b] | DTaP -IPV [c] | DTaP -IPV [d] | 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 |
| 2015 | 2009 | 91.9 | 2.2 | 94.1 | 2004 | 92.7 | 92.7 | 2000 | 61.0 |

* 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 Percentage of the total cohort. In 2011 universal hepatitis B vaccination was introduced; risk groups were vaccinated previously.
b Revaccinated toddlers.
c Toddlers that reached basic immunity at age 2-5 years and were therefore not eligible for revaccination at toddler age.
d Sufficiently protected toddlers (sum of b and c).

## 2.4 Literature

1*. van Lier EA, Oomen PJ, Giesbers H, Conyn-van Spaendonck MAE, Drijfhout IH, Zonnenberg-Hoff IF, et al. Immunisation coverage of National Immunisation Programme in the Netherlands: Year of report 2015. Bilthoven: RIVM, 2015 RIVM report 2015-0067.

* RIVM publication

# 3
# Burden of disease

*E.A. van Lier, S. McDonald, B. de Gier, M. Bouwknegt, T.M. Schurink-van 't Klooster, I. Veldhuijzen, N.A.T. van der Maas, L. Mollema, S. Hofstraat, J. Wallinga, H.E. de Melker*

## 3.1 Key points

- The estimated average annual disease burden expressed in Disability Adjusted Life Years (DALYs) for the period 2010-2014 was, from high to low: invasive pneumococcal disease (8,746 DALYs/year), pertussis (4,337 DALYs/year), measles (1,805 DALYs/year), rotavirus infection (1,539 DALYs/year), invasive meningococcal disease (736 DALYs/year), invasive *Haemophilus influenzae* infection (482 DALYs/year), acute hepatitis B infection (402 DALYs/year), rubella (133 DALYs/year), hepatitis A infection (117 DALYs/year), rabies (15 DALYs/year), tetanus (5 DALYs/year), mumps (4 DALYs/year), diphtheria (0.5 DALYs/year) and poliomyelitis (0 DALYs/year).

## 3.2 Burden of disease

In the State of Infectious Diseases in the Netherlands, 2013 [1] national burden of disease estimates expressed in Disability Adjusted Life Years (DALYs) were presented for 32 infectious diseases in the period 2007-2011. Here we present an update for the disease burden of 13 vaccine-preventable diseases in the period 2010-2014. We used the same methodology and assumptions that were used in the State of Infectious Diseases [1, 2], except that for mumps, measles, pertussis and rubella multiplication factors to correct for underestimation (under-ascertainment and/or under-reporting) of the incidence have been updated. *Under-ascertainment* refers to the extent to which incidence is underestimated because there are cases in the community who do not contact health services (such as their general practitioner), either because their infection is asymptomatic or because they suffer from mild illness only. *Under-reporting* refers to those cases who do contact health services, but whose disease status is either incorrectly diagnosed or classified, or fails to be reported to the organisation responsible for surveillance. Additionally, we have included the estimated disease burden of rotavirus infection based on a methodology developed by Havelaar et al. [3, 4] For HPV and varicella, models to estimate disease burden are not yet available.

The total number of reported cases per year, the selected multiplication factors and the estimated average annual incident cases and deaths over the period 2010-2014 for all diseases are provided in Table 3.1. Table 3.2 gives a comprehensive overview of the national burden estimates for each of the diseases investigated, reporting several measures (Years Lived with Disability (YLD) per year, Years of Life Lost (YLL) per year, DALYs/year, DALYs per 100 infections).

The estimated average annual burden for new cases for the period 2010-2014 is depicted in Figure 3.1. For poliomyelitis, the estimated disease burden was zero because there were no cases reported in this period. For diphtheria, mumps, tetanus and rabies, the disease burden was estimated to be very low, while the highest burden was estimated for invasive pneumococcal disease, followed by pertussis, measles and rotavirus infection.

The relationship between individual-level burden (DALYs/100 infections) and population-level burden (DALYs/year) is depicted in Figure 3.2. Mumps has a relatively low burden at both the population and the individual levels. Rotavirus infection and pertussis have a relatively low burden at the individual level, whereas the disease burden at the population level is rather high due to the high incidence. In contrast, rabies, tetanus and diphtheria have a relatively high burden at the individual level, but a low burden at the population level due to the limited number of cases.

Compared with the disease burden estimated for the earlier period of 2007-2011 reported in the State of Infectious Diseases, there are some notable differences:

- The measles burden is higher because of the measles outbreak that occurred in 2013/2014 and mainly affected unvaccinated orthodox reformed individuals.
- The pertussis burden is higher because of the epidemics in 2012 and 2014, in which the highest number of cases were notified since the introduction of mandatory notification in 1975. Furthermore, a different methodology was used to derive the multiplication factor. This improved methodology estimated a higher average annual incidence of symptomatic infection, mainly due to higher symptomatic probabilities estimated for adults (40% and 35% for persons aged 20-59 and ≥60 years, respectively), compared with the symptomatic probability previously applied for all cases >9 years (25%).
- The rubella burden is higher because there was a single case of congenital rubella, which can lead to severe lifelong sequelae.

It must be noted that the total disease burden for pneumococcal disease, meningococcal disease and *Haemophilus influenzae* infection is higher than presented here because we limited our analyses to *invasive* disease. Finally, our analyses only reflect the burden of new cases of acute hepatitis B infection in the period 2010-2014, which means that the disease burden of (chronic) hepatitis B cases infected prior to this period is not included.

## 3.3 Tables and Figures

**Table 3.1** Total number of reported new cases in the years 2010-2014, multiplication factors (MFs) chosen to adjust for underestimation, and the estimated average annual number of new infections (averaged over the period 2010-2014 and adjusted for underestimation) and deaths, per disease.

| Disease | Total number of reported new cases | | | | | MF(s) chosen using Uniform or Pert distribution | Estimated annual number 2010-2014 | |
|---|---|---|---|---|---|---|---|---|
| | 2010 | 2011 | 2012 | 2013 | 2014 | | Infections | Deaths |
| Diphtheria | 0 | 1 | 1 | 0 | 1 | UE: 1[d] | 0.6 | 0.02 |
| Hepatitis A | 262 | 125 | 121 | 109 | 105 | See Havelaar et al.[3, 4] | 711 | 2 |
| Hepatitis B (acute) | 199 | 159 | 174 | 145 | 141 | UA: 1.33[c]<br>UR: Uniform (1.20,1.22)[c] | 894 | 11 |
| Invasive *Haemophilus influenzae*[a] | 143 | 139 | 140 | 159 | 160 | UE: Uniform (1.05,1.20)[c] | 167 | 13 |
| IMD[a] | 137 | 101 | 98 | 116 | 83 | UE: 1.05[c] | 112 | 12 |
| IPD[b] | 2252 | 2496 | 2472 | 2592 | 2152 | UE: Uniform (1.05,1.20)[c] | 2,692 | 404 |
| Measles | 15 | 51 | 10 | 2688 | 140 | UE: Pert(8.44,11.21,15.02)[e] | 6,612 | 24 |
| Mumps[a] | 569 | 614 | 397 | 205 | 39 | UE: Pert(1.55,1.79,2.13)[f] | 659 | 0.005 |
| Pertussis[a] | 3733 | 5450 | 13853 | 3422 | 8575 | UE: Pert(23,41,66) (<1 yr)[g]<br>Pert(17,25,34) (1-4 yrs)<br>Pert(16,26,39) (5-9 yrs)<br>Pert(6,10,15) (10-19 yrs)<br>Pert(37,47,59) (20-59 yrs)<br>Pert(49,69,96) (60+ yrs) | 250,038 | 33 |
| Poliomyelitis | 0 | 0 | 0 | 0 | 0 | - | 0 | 0 |
| Rabies | 0 | 0 | 0 | 1 | 1 | UE: 1[c] | 0.4 | 0.4 |
| Rotavirus | 5,834 | 3,947 | 3,363 | 3,913 | 1,607 | See Havelaar et al.[3, 4] | 284,906 | 44 |
| Rubella | 0 | 3 | 1 | 57 | 2 | UE: Pert(8.44,11.21,15.02)[e]<br>(MF measles used as proxy) | 143 | 0.2 |
| Tetanus | 1 | 6 | 2 | 1 | 0 | UE: Uniform(1.0,1.41)[c] | 2 | 0.2 |

UA = under-ascertainment, UR = under-reporting, UE = underestimation (UA + UR combined), IMD = invasive meningococcal disease, IPD = invasive pneumococcal disease

a Cases with unknown age and/or sex were imputed using the univariate method.
b Corrected for 25% coverage of the sentinel surveillance system.
c Same multiplication factor as used in State of Infectious Diseases in the Netherlands, 2013 [1].
d No multiplication factor available.
e New multiplication factor based on random effects meta-analysis of data from measles outbreaks in 1999/2000 [5] and 2013/2014 (preliminary data).
f New multiplication factor based on random effects meta-analysis of data from mumps outbreaks in 2009/2010 [6] and 2012 [7].
g New multiplication factor derived by evidence synthesis approach [8].

**Table 3.2** Estimated average annual burden in the period 2010-2014 for new cases in this period: mean (with 95% uncertainty intervals) YLD/year, YLL/year, DALYs/year, and DALYs/100 infections.

| Disease | YLD/year | YLL/year | DALYs/year | DALYs/100 infections |
|---|---|---|---|---|
| Diphtheria | 0.01 (0.01-0.01) | 0.48 (0.39-0.56) | 0.49 (0.40-0.57) | 81 (67-95) |
| Hepatitis A | 42 (29-66) | 75 (45-124) | 117 (76-187) | 17 (13-21) |
| Hepatitis B (acute) | 204 (203-205) | 198 (178-216) | 402 (382-421) | 45 (43-47) |
| Invasive *H. influenzae* | 113 (103-123) | 370 (347-392) | 482[a] (458-508) | 289 (275-304) |
| IMD | 53 (43-65) | 682 (551-834) | 736[b] (593-898) | 654 (596-709) |
| IPD | 138 (136-140) | 8,608 (8,098-9,109) | 8,746 (8,237-9,248) | 325 (307-343) |
| Measles | 157 (139-176) | 1,648 (1,182-2,128) | 1,805 (1,336-2,290) | 27 (20-34) |
| Mumps | 3.3 (3.1-3.4) | 0.3 (0.2-0.4) | 3.6 (3.4-3.8) | 0.5 (0.5-0.6) |
| Pertussis | 2,626 (2,520-2,733) | 1,711 (1,532-1,915) | 4,337 (4,087-4,605) | 1.7 (1.7-1.8) |
| Poliomyelitis | 0 | 0 | 0 | n.a. |
| Rabies | 0.01 (0.01-0.02) | 15 (15-15) | 15 (15-15) | 3,729 (3,729-3,729) |
| Rotavirus | 1,027 (340-2,234) | 512 (393-658) | 1,539 (837-2,752) | 0.51 (0.32-0.95) |
| Rubella | 114 (91-140) | 19 (15-23) | 133 (106-162) | 93 (74-113) |
| Tetanus | 0.05 (0.05-0.06) | 5.0 (4.6-5.4) | 5.1 (4.6-5.5) | 210 (199-221) |

YLD = Years Lived with Disability, YLL = Years of Life Lost, DALYs = Disability Adjusted Life Years, IMD = invasive meningococcal disease, IPD = invasive pneumococcal disease

a Proportion caused by the vaccine-preventable type b: 29%,

b Proportion caused by the vaccine-preventable type C: 3%; proportion caused by type B: 82%.

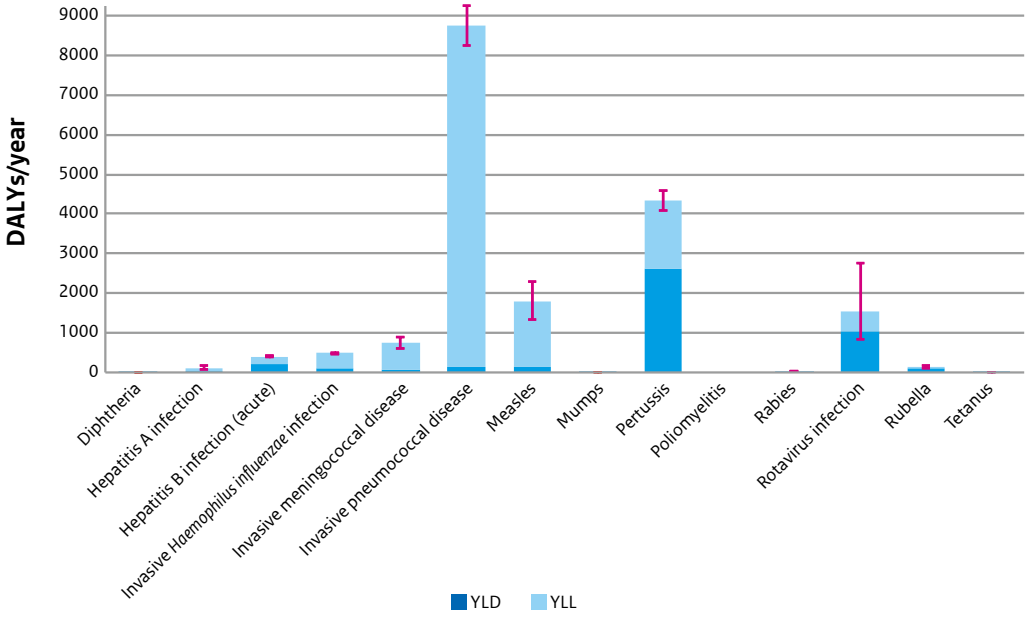


**Figure 3.1** Estimated average annual burden in the period 2010-2014 for new cases in this period, with the Years Lived with Disability (YLD) and Years of Life Lost (YLL) components shown separately.

Note 1: red lines indicate 95% uncertainty intervals.
Note 2: for the three invasive diseases, there was only a vaccine available against certain serotypes in the period 2010-2014: *Haemophilus influenzae* serotype **b (Hib),** meningococcal **C** and pneumococcal serotypes **4, 6B, 9V, 14, 18C, 19F, 23F** and, from 2011 onwards, also serotypes **1, 5, 7F.**

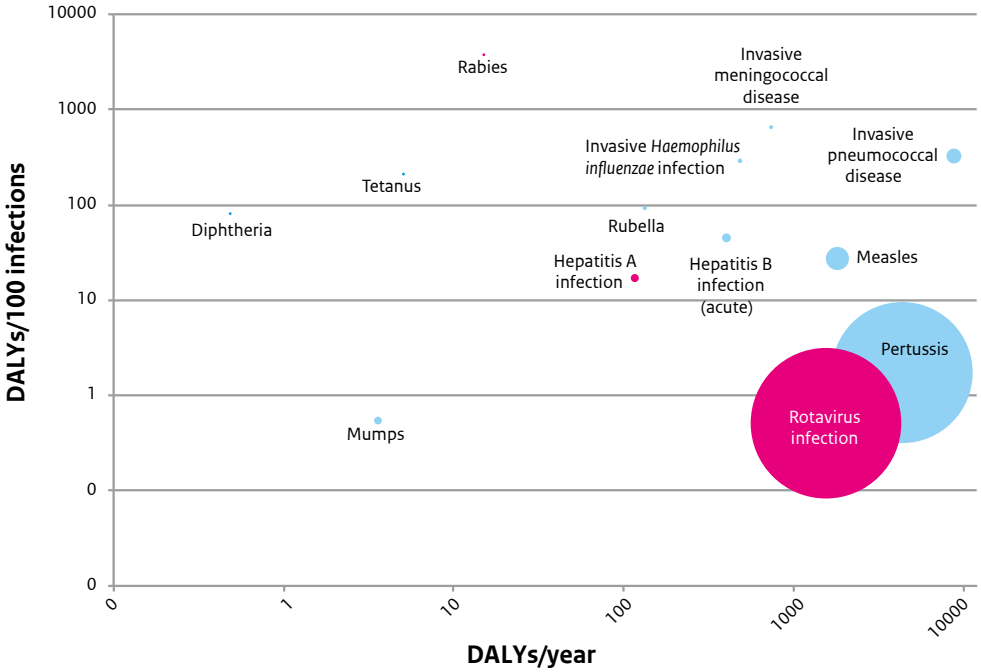


**Figure 3.2** Ranking of diseases by estimated average annual burden at population (DALYs/year) and individual level (DALYs/100 infections) in the period 2010-2014; poliomyelitis could not be included because there were no cases reported in this period.
The area of each bubble is proportional to the average number of estimated annual cases (100 cases were added to each bubble to aid visibility).

Note 1: both axes are on a logarithmic scale.
Note 2: blue bubbles = included in NIP, orange bubbles= not included in NIP.
Note 3: for the three invasive diseases, there was only a vaccine available against certain serotypes in the period 2010-2014: *Haemophilus influenzae* serotype **b (Hib)**, meningococcal **C** and pneumococcal serotypes **4, 6B, 9V, 14, 18C, 19F, 23F** and, from 2011 onwards, also serotypes **1, 5, 7F.**

## 3.4 Literature


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* RIVM publication

# 4
# Acceptance of vaccination and communication

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## 4.1 Key points

- The acceptance of vaccination will be monitored using a system consisting of information from the public, professionals and social media.
- RIVM has started to conduct research on the perception of vaccines not included in a public vaccination programme in order to be able to develop communication materials for the public and professionals to help them make a well-considered decision on whether to vaccinate or not.
- The intention to vaccinate against HPV was lower among groups originating in Surinam, the Netherlands Antilles and Aruba (47%), the Middle East and North Africa (30%), and Sub-Saharan Africa (37%) compared with the indigenous Dutch group (61%).
- Clinical symptoms, vaccine effectiveness and mortality are relevant in the decision-making process of older adults.
- Behavioural inoculation seemed not to be an effective strategy to induce resistance to myths on the topic of HPV vaccination.

## 4.2 Acceptance of vaccination

The average vaccination coverage in the Netherlands is high (95%). To prevent outbreaks of infectious diseases, it is essential that this level be sustained. The 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.

### 4.2.1 Monitoring system for acceptance of vaccination

The four-year SOR (Strategic Research RIVM) project (S/210086 'Setting-up monitoring system NIP') has resulted in a proposal to set-up a monitoring system for the acceptance of vaccination among parents and child vaccine providers (see link to thesis of Irene Harmsen: *http://digitalarchive.maastrichtuniversity.nl/fedora/get/guid:072c7383-8a0a-4d67-87cb-615c3217b5f5/ASSET1*) [1]. This proposed monitoring system will be evaluated and implemented in the coming years.

### 4.2.2 HPV vaccine acceptability among parents and their daughters in a multi-ethnic city, Amsterdam

Ethnic groups that may benefit most from the HPV vaccination have a lower acceptance and uptake of the HPV vaccine than the indigenous Dutch population. Research that provides estimates on HPV vaccine acceptance and uptake, and the factors associated with HPV vaccine

acceptance and uptake in these groups is needed for the design of effective public health interventions.

In Amsterdam, a multi-ethnic city, we invited all girls and their parents/guardians to participate in a study on HPV vaccine acceptance. The invitation was restricted to parents/guardians of girls that were invited for the HPV vaccination in 2014. The analyses of the questionnaire data on girls are not yet finished. In total, 33% of the parents/guardians, mostly mothers, completed the questionnaire on HPV vaccine acceptance. The ethnicities of respondents were grouped by region-of-origin: parents/guardians from (i) the Netherlands, (ii) Surinam, the Netherlands Antilles and Aruba, (iii) the Middle East and North Africa, (iv) Sub-Saharan Africa, (v) Europe, and (vi) Other. Among the participating parents, the intention to have their daughter vaccinated against HPV was high in the Dutch group (61%, indicating they certainly wanted to vaccinate their daughter against HPV), and lower in the other groups: 47% in the Surinamese group, 30% in the group with origins in the Middle East and North Africa, 37% in the group originating in sub-Saharan Africa, 59% among those originating from other European countries and 52% in Others. This intention was significantly lower in the first three groups compared with the Dutch group. Lower intention-to-vaccinate against HPV in non-Dutch ethnicities in Amsterdam can be largely explained by differences in crucial social-psychological factors between ethnic groups. More in-depth analyses are planned to determine the most important social-psychological factors and to discuss possible interventions for increasing vaccine uptake in these risk groups.

### 4.2.3 Interventions to increase vaccine uptake

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

This year a randomised controlled trial has been conducted to examine whether an interactive web-based, tailored Decision Aid (DA) 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 results in a higher vaccination uptake compared with the education usually provided. The study took place between January and March 2015 before the first HPV vaccination round. Mothers of girls to be invited for the HPV vaccination in 2015 received an invitation to participate in the study via Praeventis and via Internet panels. Those who gave an informed consent to participate in the study were randomized into one of the following conditions: experimental (i.e. a link to the tailored DA) or control group (i.e. no information). The DA consisted of a website providing tailored feedback on the following HPV vaccination themes: facts and rumours on the vaccination, vaccine effectiveness, risk of getting HPV and cervical cancer, what other mothers do, side effects of the vaccination, protective methods for cervical cancer, the developmental stages from HPV to cervical cancer. Furthermore, mothers were able to weigh the pros and cons of the HPV vaccination in a decisional balance. Mothers were guided through the DA by means of two virtual assistants; a mother-like assistant was used to help mothers navigate through the DA, and a female doctor-like assistant was used to deliver tailored feedback about the HPV vaccination.
More than 4,000 mothers completed the RCT study. Results are currently being examined via data analyses and are expected in 2016.

### 4.2.4 The effect of media attention on the use of injection needles that possibly contain glue and/or plastic particles on the vaccination intention of mothers of girls to be invited for the HPV vaccination

This year data has been collected by means of a Randomized Controlled Trial (RCT; see Section 4.2.3 for information) among mothers of girls to be invited for the HPV vaccination. This data included attitudes and intentions towards the HPV vaccination. At the start of the HPV vaccination campaign in March 2015, media messages appeared about the use of injection needles that possibly contain glue and/or plastic particles, and the consequences of this for human health. These injection needles were also used in the NIP. The government decided to stop the use of these injection needles until further research indicated they were safe. An experiment was therefore conducted on the effects of media attention on the attitudes and intentions of mothers regarding the HPV vaccination of their daughter. This experiment was performed among a subsample of the afore mentioned RCT (Section 4.2.3). Of the invited mothers (N = 462), 348 (75%) completed the third survey. Results are currently being examined via data analyses and are expected in October 2015.

### 4.2.5 Determinants of students' willingness to accept a MMR booster vaccination during a mumps outbreak

In 2012, during the mumps epidemic, university students filled in a questionnaire developed to assess their willingness to accept a MMR booster vaccination [2]. Of these participants, 60% would be willing to accept the hypothetical booster vaccination. Especially those students who perceived mumps as a serious disease, who expected the vaccination to prevent individual illness and who believed their own vaccination would help stop the epidemic were willing to accept an extra vaccination.

### 4.2.6 Maternal pertussis vaccination

Pertussis vaccination during pregnancy has been implemented in several countries (the United States, the United Kingdom, Belgium) with good effectiveness and no adverse safety signals to date [3-5]. In the Netherlands, van Lier et al. conducted a questionnaire survey to assess parental attitudes towards the implementation of new vaccines in the NIP, e.g. varicella vaccination [6]. Part of this survey was to measure the acceptance of pertussis vaccination during pregnancy (unpublished data). Sixty-one per cent of the participating parents (n=491) said they would accept pertussis vaccination during pregnancy if this would protect their infant against whooping cough. A slightly higher percentage of participants (64%) would accept maternal pertussis vaccination directly after birth to protect the newborn, while 55% of the participants would vaccinate their newborn directly after birth for protection.

### 4.2.7 Vaccines not included in a public vaccination programme

RIVM has started to conduct research on the perception of vaccines not included in a public vaccination programme (e.g. chickenpox, gastroenteritis caused by rotavirus infection and shingles) in order to be able to develop communication materials for the public (e.g. children, adults and the elderly) and professionals (e.g. child vaccine providers, general practitioners, paediatricians) to help them make a well-considered decision on whether to vaccinate or not. At the moment, there is little information on these vaccines, which might be one of the

reasons for underutilisation [7]. Research will consist of literature searches and qualitative and quantitative studies.

### 4.2.8 Acceptance of vaccination among Dutch older adults

Insight into the determinants that older adults take into account in their vaccination decision-making process is crucial to provide them with adequate information and to predict the uptake of vaccines in this specific group. Much information is already known about the different factors that are important; but there is a lack of knowledge on the relative importance of these factors. A discrete choice experiment was conducted to obtain this information. A set of two choices each is presented to the respondents, with each choice consisting of a vaccine containing different characteristics. In our experiment, the clinical symptoms, mortality rate of the infectious disease, the susceptibility for a certain disease, the vaccine effectiveness, side effects of the vaccine and the number of vaccinations needed varied between the choices. With respondents favouring one choice over the other, vaccine preferences are revealed. Concerning vaccine and disease characteristics, pneumonia symptoms (vs influenza symptoms), 100% vaccine effectiveness (vs 50% effectiveness), 100% susceptibility (vs 1% susceptibility) and protection against a disease with 20% mortality (vs 1% mortality) were significantly revealed as vaccine preferences in the vaccination decision-making of older adults. Symptoms of pertussis and herpes zoster (vs influenza symptoms), side effects (mild vs severe) and the number of vaccinations (1 vs 2 doses) were considered less important. These results give leads for the communication strategies used when these vaccines are implemented. Expected vaccination acceptance rates were 56% for pneumococcal disease and 45% for both pertussis and herpes zoster vaccination.

## 4.3 Communication of NIP

### 4.3.1 Behavioural HPV inoculation experiment

Anti-vaccination messages are widespread on the Internet and might negatively influence a parent's vaccination decision.
Recently, a behavioural inoculation experiment was conducted to find out whether this is an effective communication strategy to induce resistance towards these negative Internet messages about HPV vaccination. The inoculation strategy [8] is a communication tool that posits that individuals can be made resistant to persuasive attacks by exposing them to weak arguments against their current attitude, including a refutation of these arguments (McGuire, 1961).
An online two-phase experiment with three conditions was carried out among 390 parents and guardians of 12 and 13 year-old girls. Phase 1 consisted of a baseline measurement. In addition, during phase 1 participants in condition 1 were asked to read a message written according to the principles of behavioural inoculation and participants in condition 2 were asked to read the mini-magazine that is currently used by the RIVM to inform parents about the HPV vaccination. Condition 3 was the control condition, they did not receive any information.
Seven days after the participants completed phase 1, participants read a persuasive attack in the form of an Internet message that was critical of the vaccine and filled out the follow-up measurement (phase 2).

The results showed that behavioural inoculation is not an effective strategy to induce resistance to myths on the topic of HPV vaccination. The behavioural inoculation treatment was less effective than the currently used HPV mini-magazine and only slightly more effective than not giving any additional information to the parents. In addition, the results suggest that the persuasive attack was responsible for the negative attitude change among parents. This finding indicates that more attention needs to be paid to strategic communication interventions that induce resistance towards negative media messages on the topic of HPV vaccination.

### 4.3.2 Communication with the public and professionals

There is a new NIP website for the public (*www.rvp.nl*) and next year the website for professionals will be adapted. A media strategy for HPV has been developed that consists of an article containing objective information about the risks and benefits of HPV vaccination in regional newspapers in cooperation with the municipal health services, an HPV story incorporated into a TV series for teenagers and HPV messages on social media where teenagers are present (e.g. Instagram).

## 4.4 Literature


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* RIVM publication

# 5
# Adverse events

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## 5.1 Key points

- In 2014, Lareb received 982 reports concerning a total of 1,950 AEFI, which is a decrease of almost 20% compared with 2013.
- The spectrum of reported AEFI is mostly in line with previous years.
- No signals emerged indicating that vaccines used in the NIP would be unsafe.

## 5.2 Passive surveillance system

The enhanced passive surveillance system, managed by Lareb, receives reports of AEFI for all vaccines included in the NIP.
In 2014, Lareb received 982 reports concerning a total of 1,950 AEFI (Table 5.1) [1]. Compared with 2013, this was a decrease of almost 20%. Of the reports, 78 (7.9%) were classified as serious.
Table 5.2 summarizes the adverse events per vaccination moment. 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. Again, the most (n=205) reported adverse events – 'injection site reactions' – occur in 4-year-old children after the administration of the fifth DTP-IPV vaccine (Infanrix-IPV®) with 'extensive limb swelling' (ELS) as an remarkable phenomenon (n=76). In 2013, this ELS was also reported in 11 children that received the DT-IPV vaccine at 9 years of age. This trend continued in 2014 (n=10). Besides that, the increase in the number of reports after vaccination at the age of 9 (42 in 2012 vs. 78 reports in 2013 and 108 reports in 2014) is also remarkable. The results of a reactogenicity study on this signal are expected in 2016.
In 13-year-old girls, Lareb received in 2013 fewer reports of chronic fatigue after a sudden rise in reports of this condition in 2012 (24 reports in 2013 vs 46 in 2012). This decline continued in 2014 (n=13; Table 5.2). The occurrence of long-lasting fatigue will be further monitored in the Netherlands in two studies conducted by the RIVM and Lareb, respectively.

## 5.3 International developments

### 5.3.1 Vaccines targeting diseases included in the current NIP

#### *5.3.1.1 DTaP-IPV-Hib-HBV*

One study evaluated whether maternal Tdap vaccination during pregnancy was associated with increased risks of adverse obstetric events or adverse birth outcomes [2]. This retrospective observational cohort study showed that, in women with singleton pregnancies that ended in live birth, receipt of Tdap during pregnancy was not associated with an increased risk of hypertensive disorders of pregnancy or preterm births or small-for-gestational age births. However, a small but statistically significant increased risk of chorioamnionitis diagnosis was observed.

A Phase IV study which assessed the safety and reactogenicity of a new DTwP-HBV-Hib vaccine found that this vaccine has a similar safety profile to that of Tritanrix (GSK Beecham) in Indian infants [3]. A comparison of DTaP and DTwP vaccines in infancy showed, however, that DTaP vaccines were found to cause fewer local, systemic and febrile reactions than DTwP vaccines [4]. In an open-label, randomized, controlled study, Iro showed that the use of different limbs for the administration of sequential doses does not influence the proportion of infants who had adverse events (AEs) [5]. Also, syringe types and needle diameter played no role in precipitating the AEs following DTwP immunization in children aged 2 months to 6 years [6]. Canada replaced the pre-school booster vaccination from DTaP-IPV to Tap-IPV in May 2012. This replacement resulted in a decline in the number of reports and AEFI reporting rates, most notably a substantial decrease in injection site reactions [7]. Marshall et al. showed that Tdap5, which is licensed for use in children beginning at 11 years of age, is as safe and immunogenic in 10-year-olds as it is in 11-year-olds [8]. These data support the conclusion that Tdap5 is safe in 10-year-olds. Carlsson conducted two consecutive randomised controlled pertussis booster trials in children initially vaccinated in infancy with an acellular vaccine: The first with a five component Tdap vaccine to 5-year-olds and the second with five component or monocomponent Tdap vaccines at the age of 14-15 years [9]. A large swelling or redness of more than half of the upper arm circumference was reported in 8/475 5-year-olds and in 6/230 15-year-olds. The frequency of AEs was nevertheless low in both preschool children and adolescents. The results of a Phase II trial also support co-administration of Tdap-IPV and HBV to adolescents and suggest that vaccination with Tdap-IPV can offer protection for 10 years after an adolescent booster vaccination [10]. In a phase III clinical trial, Han et al. demonstrated a good safety profile of a new Td vaccine in healthy adolescents [11].
Vandermeulen et al. showed that decennial booster vaccination with combined, reduced dTap vaccines (containing 0.5 or 0.3 mg of aluminium) are well-tolerated in young adults [12]. Similar results were found in a phase IV study among healthy adults [13]. A multicentre study assessed the safety of one dose of Tdap-IPV followed by two doses of Td-IPV in adults who had not received a DT-containing vaccine in the last 20 years [14]. More AEs were reported following vaccination with Tdap-IPV than with Td-IPV. However, both vaccines were well-tolerated. Mayet presented the results of a surveillance of vaccine AEs reported from 2011 to 2012 in the French armed forces [15]. High rates of AEs were observed for dTap-IPV (106.1 per 100,000 doses) and MenACWY-CRM (39.3 per 100,000 doses). However, AEs appear to be relatively rare, particularly serious AEs, which indicates an acceptable tolerance of vaccines.

#### *5.3.2.1 Hepatitis B*

Sharma investigated the persistence of serum antibodies against hepatitis B surface antigens 3.1-3.5 years following primary vaccination with 3 doses of HBvacPro→ in healthy adults aged ≥50 years [16]. The safety profile of HBvacPro→ challenged with 1 dose of recombinant hepatitis B antigen was consistent with the well-established safety profile of the vaccine HBvaxPro→. Avdicova et al. showed that administration of HBV challenge dose 10-11 years after the 3, 5, 11-12 months primary schedule was well-tolerated [17]. In a randomised trial, the safety of a recombinant hepatitis B vaccine was assessed in adult dialysis and pre-dialyses patients [18]. There were 22 serious AEs; none were considered to be related to the study vaccine. Gaggar studied GS-4774, a hepatitis B virus-specific therapeutic vaccine [19]. The

results showed that GS-4774 was safe and well-tolerated in healthy adults with injection site reactions being the most frequently reported AEs. Further evaluation of GS-4774 is ongoing in patients with chronic HBV infection.
Hieu et al. evaluated the safety of thiomersal-free and thiomersal-containing vaccines in healthy neonates [20]. Both formulations were well-tolerated although there was evidence that the thiomersal-free vaccine was associated with fewer local AEs. No serious AEs were reported during the study. However, in a hypothesis testing case-control study, Geier et al. found that cases diagnosed with specific delays in development were significantly more likely than controls to have received increased organic mercury from thimerosal-containing hepatitis B vaccine administered in the first, second and sixth month of life [21]. Data from a murine model support the concept that different components of hepatitis B vaccines may be linked with immune and autoimmune mediated AEs [22]. The same author analysed the medical records of 19 patients with chronic fatigue syndrome and/or fibromyalgia following HBV vaccination. The results suggest that, in some cases, these disorders can be temporally related to immunisation as part of autoimmune syndromes induced by adjuvants (ASIA). ASIA criteria were fulfilled in all patients eluding the plausible link between ASIA and the disorders [23]. However, current studies of ASIA are so diverse that there is currently a lack of reproducible evidence for any consistent relationship between adjuvant and autoimmune conditions [24]. The addition of a mandatory criterion requiring temporal association and clinically relevant adjuvant dose would allow a better definition of what constitutes a diagnosis of ASIA. For the NIP, these results have no consequences, since thimerosal is not used as a preservative in routinely recommended childhood vaccines in the Netherlands.

#### *5.3.1.3 MMR*

Several studies examined the safety of the MMR vaccine. Evidence was found that this vaccine is associated with already known serious AEs such as febrile convulsions [25] and anaphylaxis [26]. But these events are extremely rare. Also, in adults no new or unexpected safety concerns for MMR vaccination were detected [27]. Furthermore, other studies suggested that vaccines could have non-specific effects on mortality, depending on the type of vaccine. Schurink et al. investigated whether there are differences in gender-specific mortality among Dutch children according to the last vaccination received. No differences were found in gender-specific mortality related to the MMR ± MenC vaccination [28].
One study evaluated whether the safety of the MMR vaccine delivered to infants by a disposable-syringe jet injector was non-inferior to that administered by needle and syringe [29]. The results showed that most AEs were mild or moderate. Crying after injection was more frequent in the needle and syringe group, and local skin reactions were more common in the jet injector group. Five serious AEs were judged to be causally unrelated to treatment and all were resolved.

#### *5.3.1.4 Meningococcal C disease*

Several phase III studies demonstrated the safety of a single dose of the MenACWY-CRM vaccine in different age-groups [30-34], or administered concomitantly with a hepatitis A and/or B vaccine [35] or 4CMenB vaccine [36]. When given as a booster, 5 years after the initial vaccination, also no safety concern was raised [37], suggesting that 5 years may be an

appropriate interval to revaccinate children. A two-dose series of MenACYW-D given concomitantly with the DTaP-IPV-Hib booster dose at 18 months of age also demonstrated a good safety profile [38]. A similar result was found for children primed with three doses of HibMenCY-TT, who then received a single dose of MenACWY-TT or a fourth dose of HibMenCY-TT [39]. These data provide support that MenACWY-TT, given with or without the fourth scheduled dose of DTaP, could be administered as an alternative to a fourth dose of HibMenCY-YY in the second year of life. In such a case, the fourth Hib dose should be administered as either a monovalent or combination Hib vaccine.
The routine booster DTaP has an acceptable safety profile when co-administrated with the MenACWY-TT vaccine in HibMenCY-TT-primed toddlers [40]. The CRM or TT-conjugated MenACWY vaccine in teenagers primed with different meningococcal conjugate vaccines at pre-school age were also well-tolerated with no attributable serious AEs [41]. In laboratory workers, no safety concerns were reported for the Hib/MenC-TT vaccine, with minor local reactions being reported by 21 % of the subjects [42]. This provides evidence that this vaccine may be used for providing protection in an occupational setting.
Two phase II studies assessed the safety and reactogenicity of investigational formulations of meningococcal serogroups ABCWY vaccines [43, 44]. Both formulations had acceptable reactogenicity profiles, with no safety concerns identified. In another phase II trial, the safety of a heptavalent combination vaccine administered to infants at 2, 4 and 12 months of age was compared with those of licensed control vaccines [45]. No differences in safety and reactogenicity profiles were detected between the groups.

#### 5.3.1.5 *Pneumococcal disease*

A post-licensure study which was conducted to assess the safety of 7-valent pneumococcal vaccination (PCV7) in catch-up regimes in previously unvaccinated older infants and young children in China demonstrated the safety of this vaccine [46]. A new heptavalent conjugate vaccine (PCV7-TT) was also well-tolerated and was as safe as a 10-valent pneumococcal vaccine (PCV10), which was used as a control vaccine [47]. PCV10, co-administered with routine childhood vaccines, were also shown to be safe in infants [48-50] and in a two-dose 10valent pneumococcal, nontypeable Haemophilus influenza protein D conjugate vaccine (PHiD-CV) catch-up regimen in the second year of life [51].
In an analysis of paediatric spontaneous reports, Trotta observed a trend towards increased risk of neurological events or convulsions following 13-valent pneumococcal vaccination (PVC13) used in routine practice, although, given the methodological limitations, these findings cannot be conclusive and require further investigations [52]. Wysocki found that, in 3 catch-up schedules with PCV13, a trend was present towards greater local tenderness with increasing age and subsequent dose administration, although, when comparing the three schedules, similar tolerability and safety profiles were found [53]. PCV13 was also well-tolerated as a follow-on dose in children previously vaccinated with 4 doses of either PCV7 or PCV13 [54].
A phase III trial showed that the addition of polysorbate 80 (P80), a non-ionic detergent used to solubilise proteins, to PCV13 did not adversely affect PCV13 safety when compared with vaccine formulated without P80 [55].
An observational study among the elderly showed a good safety and tolerability of PCV13 in routine clinical practice, further confirming the evidence coming in from clinical trials in the

same age-group [56, 57]. In HIV-infected adults, paediatric patients with inflammatory bowel disease and children with sickle-cell disease previously vaccinated with 23-valent pneumococcal polysaccharide vaccine (PPSV23), PCV13 was shown to be safe [58-60].
A three-dose regimen of PCV13 followed by one dose of PPSV23 was well-tolerated in pneumococcal vaccine-naïve, HIV infected individuals [61] and in patients after hematopoietic stem cell transplant, although dose 4 was associated with increased local and systemic reactions [62].
In an open-labelled randomised study among elderly people aged 80 or older, PPSV23 and PCV7 were tolerated without any severe adverse events, although adverse reaction such as redness and localised swelling were more common in the PCV7 group [63]. The PPSV23 also had a good tolerability in 2 to 70 year-old healthy people [64] and in juvenile idiopathic arthritis patients [65]. When co-administrated with an adjuvanted trivalent inactivated influenza vaccine, local and systemic AEs were more common in subjects receiving PPSV23 and influenza vaccination simultaneously, compared with those receiving the influenza vaccine alone [66].
New vaccines are being developed to provide broader protection against pneumococcal disease. Investigational vaccine formulations containing detoxified pneumolysin (dPly) and pneumococcal histidine triad D (PhtD) were well-tolerated when administered to healthy adults as stand-alone protein vaccine or combined with PHiD-CV conjugates [67]. A 15-valent pneumococcal conjugate vaccine was evaluated in healthy adults. PCV15 displayed an acceptable safety profile, although higher frequencies of erythema, swelling and myalgia were reported among PCV15 versus PCV7 recipients [68].

#### *5.3.1.6 HPV*

Several studies were conducted into the safety of HPV vaccines. An acceptable safety profile was reported for the bivalent HPV vaccine (HPV2) up to 4 years after the first vaccination [69]. Also, the quadrivalent HPV vaccine (HPV4) was generally well-tolerated [70], although the reporting rates of syncope or loss of consciousness and seizures were higher for the HPV4 vaccine than for other vaccines given in adolescence [71]. When given as a booster, both vaccines were shown to have an acceptable safety profile [72]. Comparing the safety of 2 doses of the bivalents HPV vaccine vs. 2 or 3 doses of the quadrivalent HPV vaccines in girls aged 9-14 years showed that the reactogenicity and safety were in line with the known profile of each vaccine [73]. However, there was a tendency towards a higher incidence of local injection site reactions in girls administered 2 doses of the bivalent vaccine than was the case in those administered 2 or 3 doses of the quadrivalent vaccines. Also, in HIV-infected adolescents, HPV4 was generally safe and well-tolerated [74], and bivalent HPV vaccine was well-tolerated in juvenile idiopathic arthritis patients [75]. Post-licensure monitoring data with a follow-up of up to 9.4 years post-vaccination indicates that both vaccines are safe [76-80]. This is confirmed in a review about the safety of HPV vaccines [81]. Furthermore, in women older than the main population for prophylactic HPV vaccines, HPV4 and the bivalent HPV vaccine had a clinically acceptable safety profile [8285].
However, along with the introduction of the HPV vaccines, several cases involving the onset of exacerbations of autoimmune diseases following the vaccine shot have been reported in the literature and pharmacovigilance databases. In the past year, several studies were conducted

into the relationship between HPV vaccines and autoimmune diseases. In a case report, Poddighe described a girl with pseudo-neurological syndrome that occurred shortly after the administration of the bivalent HPV vaccine [86]. It was supposed to be ASIA, given the temporal link with vaccination and the presence of anti-phospholipid autoantibodies. No causal relationships were found between HPV4 and demyelinating diseases [87] nor between bivalent HPV and migraine [88], although in the latter study the number of cases was low. Pellegrino [89] analysed comprehensively all case reports and studies dealing with either the onset of an autoimmune disease in vaccinated subjects or the safety in patients with autoimmune diseases in order to define the role of the HPV vaccines in these diseases and hence their safety. They concluded that solid evidence of a causal relationship was provided in a few cases in the examined studies and the risk vs. benefit of vaccination has still to be solved. So, although there is no evidence of statistical association with many post-vaccination events, the ongoing vigilance with respect to the safety of these vaccines remains important. The European Medicines Agency (EMA) has started a review of HPV vaccines to further clarify aspects of their safety profile. This review will look at available data with a focus on rare reports of two conditions: complex regional pain syndrome and postural orthostatic tachycardia syndrome. Reports of these conditions in young women who have received an HPV vaccine have been previously considered during routine safety monitoring. It will now be reviewed whether the number of cases reported with HPV vaccine is greater than would normally be expected. If so, the EMA will decide whether to recommend any changes to product information to better inform patients and health care professionals.
A nonavalent human papillomavirus (9vHPV) vaccine has been developed to prevent infections and diseases related to HPV 6/11/16/18 (as per the licensed quadrivalent HPV vaccine), as well as 5 additional oncogenic HPV types (HPV 31/33/45/52/58). The 9vHPV and HPV4 vaccines showed comparable safety profiles, although the incidence of injection site swelling was higher in the 9vHPV vaccine group [90]. Other studies also showed that 9vHPV was generally well-tolerated [91-93].

### 5.3.2 Other possible future NIP candidates

#### 5.3.2.1 *Varicella*

Four studies showed that the administration of MMRV has an acceptable safety profile in children 12 to 23 months of age, although a small increased risk of fever and rash [94], and febrile seizures following the first dose of MMRV were found as compared with MMR+V [95, 96]. MMRV-related injection site reactions occurred more frequently when given concomitantly with a hexavalent vaccine. However, the safety profile was in line with that of the individual Summaries of Product Characteristics [97]. Bechini et al. evaluated the impact of varicella vaccination on the incidence and hospitalizations due to varicella and its complications in the period 2003-2012 in Italy [98]. They concluded that AEs due to varicella vaccines are rare and without permanent sequelae, so solid evidences in support of universal varicella vaccination arise from the experiences available in Italy. Macartney et al. concluded that monovalent varicella vaccine at age 18 months is not associated with an increased risk of febrile convulsions [99].

In a phase III trial conducted to evaluate the safety and tolerability of a freeze-dried live attenuated Oka strain Varicella vaccine, it was shown that AEs in this test vaccine were not different from the control group receiving Varilrix [100]. The safety of Varilrix in adults who had undergone autologous hematopoietic stem cell transplantation was shown by Sasadeuasz [101], although Grade 3 solicited AEs that were causally related to vaccination were reported by 44.8% of the patients after dose 1 and by 10.3% of the patients after dose 2. However, no major safety signals were detected.

#### *5.3.2.2 Herpes zoster*

The safety of herpes zoster vaccination was demonstrated in healthy adults [102], as well as in adults on chronic/maintenance corticosteroids [103]. A randomised non-inferiority clinical trial demonstrated that, in adults aged ≥50 years, intramuscular administration of zoster vaccine was well-tolerated, with fewer injection site reactions than with subcutaneous administration [104]. However, a case report by Bhalla et al. described the fatality of an immunocompromised patient who received the varicella vaccine [105]. Within 3 months of vaccination, this patient developed recurrent rashes with fever, malaise, weakness, hepatitis, weight loss, and renal failure. This syndrome was eventually determined to be associated with persistent disseminated zoster caused by the vaccine virus. This case illustrates the concerns about the use of live attenuated vaccines in immunocompromised individuals. For such patients, a subunit vaccine may be an appropriate alternative. A phase I/II study showed the clinically acceptable safety profile of an investigational herpes zoster subunit vaccine in HIV-infected adults [106]. A phase III study confirmed this result [107]. Although solicited reports of injection site reactions and systemic reactions within 7 days after vaccination were more frequent in the vaccine group than in the placebo group, the proportions of participants who had serious AEs or potential immune-mediated diseases or who died were similar in the two groups.

#### *5.3.2.3 Hepatitis A*

The result of a 5-year follow-up phase IV study showed that a single dose of live attenuated hepatitis A vaccine is well-tolerated in healthy children [108]. Jain et al. investigated the safety of a virosomal hepatitis A vaccine compared with an aluminium-absorbed hepatitis A vaccine [109]. The overall incidence of AEs (solicited and unsolicited) after each vaccination was similar in both groups, so both vaccines were well-tolerated. Van der Meeren et al. assessed the safety profile of the inactivated hepatitis A vaccine in healthy adults aged ≥40 years compared with subjects aged 20-30 years [110]. Safety profiles were found to be similar in both groups.

#### *5.3.2.4 Meningococcal B disease*

Three studies were published about meningococcal B vaccination. In the first one, Prymula et al. indicates that by using paracetamol prophylaxis, post-vaccination reactions are reduced without clinically relevant negative consequences in vaccine immunogenicity [111].
In the second one, Esposito et al., investigated whether reducing the outer membrane vesicle (OMV) and/or protein content influences 4CMenB reactogenicity in healthy 2-month-old infants [112]. Groups with no or low-dose OMV displayed slightly lower reactogenicity profiles, but all formulations were generally well-tolerated. However, decreasing or removing the OMV content had an unacceptable negative impact on the immunogenicity profile.

#### *5.3.2.5 Rotavirus*

In general, rotavirus vaccines have a good safety profile in healthy infants [113] and in hospitalised infants [114]. Regarding intussusception, several studies were published which show that the intussusception risk after rotavirus vaccination is small and exists mainly after the first dose and marginally after the second and third dose [113, 115-117]. Escolano et al. assessed the risk of intussusception following the pentavalent rotavirus vaccine using a self-controlled case series [116]. They found an incidence risk ratio for the 3 to 7 day period compared with the risk in the 15 to 30 day period of 3.45 (95%CI 1.84-6.55), 1.63 (95%CI 0.86-3.13) and 1.73 (95%CI 0.86-3.51) after the first, second and third dose, respectively. Similar results were found by Bauchau in a post-marketing monitoring study into the association between intussusception and a monovalent rotavirus vaccine (observed-to-expected ratio 2.96, 95%CI 1.45-5.45 and 0.66, 95%CI 0.21-1.53 for 7 days post-dose 1 and post-dose 2, respectively) [115]. With a self-controlled risk interval method, Haber et al. also found in VAERS a significant increased risk of intussusception 3-6 days after dose 1 of a monovalent rotavirus vaccine (daily reporting ratio 7.5, 95%CI 2.3-24.6) [118]. The daily reporting ratio was elevated but not significant after dose 2 (2.4, 95%CI 0.8-7.5). Two other studies focused on a monovalent rotavirus vaccine did not find an increased risk [119, 120]. In France, however, because of three infant deaths and many serious side effects, rotavirus vaccines are no longer recommended for the routine immunisation of children [121]. Two of the deaths following vaccination were due to very severe forms of intussusception. The third death following rotavirus vaccination was due to necrotizing enterocolitis in an infant treated by a human varicella-zoster immunoglobulin. Furthermore, there were 508 notifications of side effects (103.8/100,000), 201 of which were serious side effects (40.9/100,000). There were also 47 intussusceptions and, among them, 14 (29.8%) required surgical treatment. Most of them occurred after the first dose and the median age for post-vaccinal intussusception was 3 months. The conclusion of the pharmacovigilance committee was that the rate of side effects was worrying when compared with other paediatric vaccines. It noted that the intussusceptions were more severe, probably, in some part, because they occurred in younger infants.

Based on post-marketing studies and post-vaccination surveillance data, the European society for paediatric infectious diseases recommends that prematurely born infants should be vaccinated according to their calendar age as recommended for full-term infants. Furthermore, they recommend that all HIV-infected or HIV-exposed infants should be vaccinated with oral rotavirus vaccine. Although specific information on many immunodeficiencies is lacking, infants with known severe combined immunodeficiency should not receive live rotavirus vaccine [122].

In the Netherlands, a recommendation by the Health Council about including rotavirus vaccination in the NIP is expected in the near future. Baseline incidences of intussusception were calculated to observe a possible increase after possible introduction (see Table 5.3 and Table 5.4). In comparison with other countries, the incidence of intussusception in the Netherlands based on International Classification of Diseases (ICD)-9 discharge codes appears to be slightly lower than rates reported in the neighbouring countries of Germany and Denmark [123-125]. Whether this reflects a truly lower incidence or incomplete coding practices is currently unknown. Furthermore, data on the severity of intussusception among Dutch

infants, including the rate of surgical procedures and resection, the occurrence of long-term sequelae or deaths, are currently lacking. Further research on this matter is needed.

Not only in children, but also in the elderly rotavirus may be an important causative agent of acute gastroenteritis. Lawrence et al. demonstrated that RV5 was generally safe and well-tolerated in healthy adults, whereby 9% of placebo recipients and 27% of RV5 recipients experienced a vaccine-related adverse event of mild or moderate intensity [126]. So, further evaluation of RV5 as a candidate vaccine in this age group may be warranted.

## 5.4 Tables and Figures

**Table 5.1** Number of AEFI-reports per dose and suspected vaccine(s)

| Vaccines | Total 2013 | Total 2014 | 2m | 3m | 4m | 11m | BMR -0 | 14m | 4yr | 9yr | 12-13yr |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Infanrix hexa® + Synflorix® | 497 | **323** | 145 | 13 | 72 | 93 | | | | | |
| Infanrix hexa® | 20 | **63** | 2 | 51 | 2 | 8 | | | | | |
| Synflorix® | 11 | **1** | 1 | | | | | | | | |
| MMRvaxPro® + NeisVac-C® | 110 | **122** | | | | | | 122 | | | |
| MMRvaxPro® | 37 | **15** | | | | | | 14 | | 1 | |
| NeisVac-C® | | **3** | | | | | | 3 | | | |
| Infanrix-IPV® | 335 | **274** | | | | | | | 274 | | |
| MMRvaxPro® + DTP-NVI | 78 | **91** | | | | | | | | 91 | |
| DTP-NVI | 11 | **16** | | | | | | | | 16 | |
| Cervarix® | 82 | **59** | | | | | | | | | 59 |
| Other | 42 | **15** | | | | | | | | | |
| Total | 1223 | **982** | 148 | 64 | 74 | 101 | | 139 | 274 | 108 | 59 |

Source: Lareb [1]

**Table 5.2** Reported adverse events per vaccination moment

| Event | Total 2014 | 2m | 3m | 4m | 11m | 14m | 4yr | 9yr | 12-13yr | Other |
|---|---|---|---|---|---|---|---|---|---|---|
| Death | **1** | 1 | | | | | | | | |
| Injection site reactions | **447** | 27 | 26 | 22 | 50 | 13 | 227 | 64 | 15 | 3 |
| Abnormal body temperature | **391** | 53 | 22 | 28 | 55 | 78 | 88 | 45 | 15 | 7 |
| Infections | **45** | 2 | 0 | 3 | 5 | 22 | 3 | 7 | 1 | 2 |
| Malaise and fatigue | **109** | 26 | 14 | 4 | 7 | 13 | 14 | 8 | 18 | 5 |
| Allergic reaction | **10** | 1 | 0 | 4 | 0 | 3 | 1 | 0 | 1 | 0 |
| Disorders of the immune system | **8** | 1 | 1 | 0 | 0 | 3 | 2 | 1 | 0 | 0 |
| Crying | **226** | 58 | 29 | 31 | 29 | 36 | 28 | 8 | 2 | 5 |
| Haematological disorders | **2** | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Gastrointestinal complaints | **155** | 25 | 13 | 9 | 11 | 23 | 18 | 27 | 25 | 4 |
| Respiratory symptoms | **19** | 7 | 2 | 3 | 1 | 1 | 1 | 2 | 2 | 0 |
| Cardiovascular diseases | **3** | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Muscle and joint disorders | **50** | 3 | 1 | 0 | 5 | 4 | 9 | 9 | 17 | 2 |
| Skin symptoms | **190** | 22 | 9 | 16 | 20 | 73 | 26 | 9 | 8 | 7 |
| Discoloured legs | **27** | 12 | 3 | 10 | 1 | 0 | 0 | 0 | 0 | 1 |
| Headache/dizziness | **89** | 0 | 0 | 0 | 0 | 0 | 13 | 43 | 30 | 3 |
| Faints | **80** | 28 | 5 | 5 | 7 | 5 | 13 | 8 | 7 | 2 |
| Fits | **37** | 6 | 2 | 2 | 4 | 17 | 4 | 0 | 1 | 1 |
| Other disorders of the nervous system | **38** | 3 | 3 | 6 | 4 | 3 | 4 | 8 | 4 | 3 |
| Other disorders | **23** | 3 | 1 | 1 | 3 | 6 | 3 | 3 | 3 | 0 |

Source: Lareb

**Table 5.3** Baseline incidences of intussusception per 100,000 per year per age*

| Age | 2008 | 2009 | 2010 | 2011 | 2012 | Mean |
|---|---|---|---|---|---|---|
| 0 years | 35.5 | 50.0 | 53.4 | 46.6 | 52.9 | **47.7** |
| 1 year | 19.2 | 28.5 | 22.4 | 25.4 | 22.1 | **23.6** |
| 2 years | 15.9 | 17.3 | 20.8 | 22.2 | 14.5 | **18.2** |
| 3 years | 12.0 | 17.1 | 14.1 | 12.1 | 11.2 | **13.3** |
| 4 years | 8.7 | 9.0 | 10.2 | 3.8 | 3.3 | **7.1** |
| 5 years | 7.9 | 5.2 | 7.7 | 2.5 | 7.3 | **6.2** |

Data source: DHD
* adjusted for the estimated decline for the national coverage of the Dutch Hospital Data of about 88% in 2008 to about 82% in 2012.
Source: Statistics Netherlands (CBS) up to 2009 and Dutch Hospital Data (DHD) from 2010 onwards.

**Table 5.4** Baseline incidences of intussusception per 100,000 per year in infants*

| Age | 2008 | 2009 | 2010 | 2011 | 2012 | Mean |
|---|---|---|---|---|---|---|
| 0-2 months | 7.5 | 19.7 | 14.6 | 20.7 | 13.7 | **15.3** |
| 3-5 months | 62.2 | 69.0 | 102.4 | 51.8 | 76.9 | **72.5** |
| 6-8 months | 49.8 | 49.3 | 36.6 | 93.2 | 74.2 | **60.6** |
| 9-11 months | 22.4 | 61.6 | 61.0 | 20.7 | 46.7 | **42.5** |

Data source: DHD
* adjusted for the estimated decline for the national coverage of the Dutch Hospital Data of about 88% in 2008 to about 82% in 2012.
Source: Statistics Netherlands (CBS) up to 2009 and Dutch Hospital Data (DHD) from 2010 onwards.

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* RIVM publication

# 6
# Current National Immunisation Programme

## 6.1 Diphtheria

*F.A.G. Reubsaet, G.A.M. Berbers, E. Swart, D.W. Notermans, N.A.T. van der Maas*

### 6.1.1 Key points

- Both in the calendar year 2014 and in 2015 up to week 22, one case of diphtheria, both cutaneous, was reported in the Netherlands.

### 6.1.2 Epidemiology

In 2014 and in 2015 up to week 22, two diphtheria notifications were received (Figure 6.1.1).

### 6.1.3 Pathogen

In 2014 and in 2015 up to week 22, the RIVM received one *Corynebacterium ulcerans* and eleven *C. diphtheriae* strains, all with the suspicion of cutaneous diphtheria. Two strains were diphtheria-toxin-PCR and Elek-test positive. Both patients had travelled abroad (Ethiopia and Indonesia, resp.), one was vaccinated, one was not.

### 6.1.4 Research

Routine surveillance through mandatory notification is in place for signal detection. Results of the PIENTER 2 study indicate long-term protection against diphtheria provided by the NIP, although antibody levels decline after vaccination. Two susceptible groups were identified.
As a result of natural waning immunity, a substantial proportion of individuals born before the introduction of diphtheria vaccination in the NIP lack adequate levels of diphtheria antibodies. Susceptibility is highest among strictly orthodox Protestants due to a lack of vaccination.

### 6.1.5 International developments

No relevant international developments have occurred in 2014 and 2015.

### 6.1.6 Tables and Figures

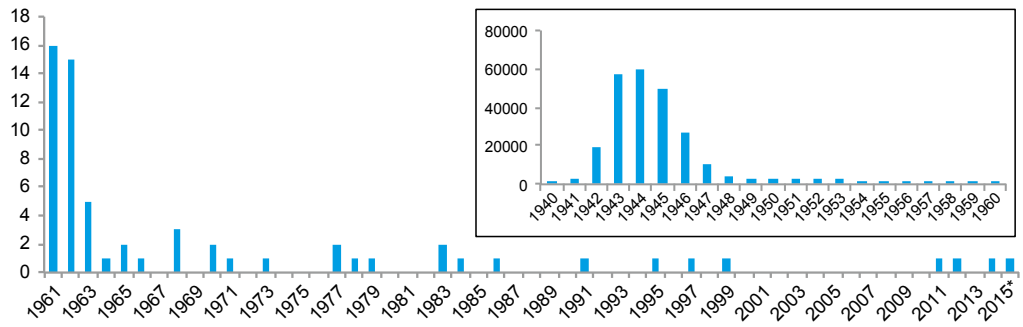


**Figure 6.1.1** Diphtheria notifications per year for 1940-1960 and 1961-2015*

* reports up to week 22, 2015 are included

## 6.2 Pertussis

*N.A.T. van der Maas, A.K. Lugnér, A.W.M. Suijkerbuijk, E.A. van Lier, A. Buisman, G.A.M. Berbers, C.A.C.M. van Els, H.E. de Melker, M. van Gent*

### 6.2.1 Key points

- Epidemic peaks of pertussis occur every two years; i.e. the incidence of pertussis notifications increased in 2014 (55 per 100,000) compared with 2013 (20 per 100,000). The incidence of pertussis notifications was not as high as in 2012 (83 per 100,000), which was the largest number since 1976 reported during a large epidemic.
- Since the introduction of acellular pertussis in the primary series, the 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 4-5 years. Thereafter, vaccinated children become more easily infected with *Bordetella pertussis*.
- A Dutch study on the acceptance of new vaccinations in the NIP showed that about 60% of parents intended to accept pertussis vaccination during pregnancy.
- The prevalence of pertactin-deficient (i.e. a component of acellular vaccines) strains was 10% in 2014, compared with 8% in 2013. In 2015, up to August, prevalence increased to 21%.

### 6.2.2 Epidemiology

#### *6.2.2.1 Disease*

Following a very low incidence of notifications in 2013, numbers in 2014 increased again (Figure 6.2.1). A slight decrease in notifications was seen in the first quarter of 2015. For age categories up to five years of age, incidence rates for 2014 were higher than in 2012, the last epidemic. For older age groups, rates were lower (Figure 6.2.2).
The hospitalisation rate showed a similar pattern: low for 2013, followed by an increase in 2014. Statistics Netherlands (CBS) reported no pertussis-related deaths in 2013 and one infant in 2014. Within the notifications, 2 deaths were reported in 2013 (1 zero-year old infant and an 88-year-old female), 2 in 2014 (1 male infant, 1 month old, and an 11-year-old vaccinated girl). In 2015 up to week 25, 1 infant too young to be vaccinated was reported to be deceased within the notifications.

#### *6.2.2.2 Vaccine effectiveness*

In Figure 6.2.3, vaccine effectiveness (VE), estimated through the 'screening method' for the infant vaccination series, is shown. We would like to emphasize that the presented VE should not be interpreted as 'true' absolute efficacies. 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 in the VE of the primary series for 1-3 year-olds [1]. In the first few years after introduction, the VE in 2 and 3 year-olds was lower compared with the current estimates because these children still received a whole-cell vaccine during infancy. From 2007 onwards, the VE in 1 to 3 year-olds remained well above 80%.

The VE for the booster dose at 4 years of age decreases after ~4 years, i.e. when children reach the age of 8 years, especially in epidemic years (Table 6.2.1).

### 6.2.3 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 haemagglutinin, 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 and 2015 (up to August), we observed an increase to 10% and 21%, respectively. In countries where acellular pertussis vaccines have been used longer than they have been in the Netherlands, prevalences of Prn-deficient strains have been found of 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 Radboudumc (Dr. D. Diavatopoulos), the efficacy of the acellular vaccines against Prn-deficient strains compared with wild type strains was studied in a mouse model. The preliminary results are indeed indicative of a lower VE when the mouse was challenged with a Prn-deficient strain [2]. These results need to be confirmed in further experiments.

### 6.2.4 Research

#### *6.2.4.1 Cellular and humoral immunity*

In humans the immune modulating effect of currently circulating pertussis strains, including vaccine antigen deficient strains, on innate immune responses is being studied. So far it has been found that *Bordetella pertussis* isolates that fail to fully activate the immune response due to alterations in their TLR4 signalling molecules occur naturally [3]. Also, other mechanisms of the waning and aging of the human specific immune response to pertussis will be studied in greater depth using clinical samples from the 'SKI-study' and it's follow-up, the 'Imm-f@ct study'. To be able to focus specifically on the long-term quality of the immune response, we recently developed an innovative T cell method at the single-cell level [4].

In a longitudinal study, we are investigating the B and T cell memory immune responses in 9-year-old children who have been 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 are monitored up to a year after the booster vaccination (KIM-study). Results are expected next year. In a second study, the long-term humoral and cellular responses of adults aged 25-29 years will be analysed after a booster vaccination with Boostrix. The participants of this so-called VIKING study have only been vaccinated in their first year of life with whole-cell vaccine. Blood has been sampled up to one year post-booster and participants will be followed up to 3 years post-booster. Results will be available in 2016.

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 on after pertussis infection appeared to increase with age [5], while the breadth of the long-term memory T cell response

was found to decrease with age [6]. This indicates that various age-related mechanisms co-occur that may influence pertussis immunity.
Although, in general, the pertussis-specific immunological responses in 6year-old Dutch 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 has also been encountered 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. To study the long-term pertussis-specific memory immunity, we have collected a longitudinal follow-up sample at more than 5 years after an extra aP pertussis booster vaccination of children 9 years of age who had been primed with a whole-cell vaccine in infancy. These samples are currently under investigation. Results are expected in 2016.

#### *6.2.4.2 Pathogen*

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 that compensate for the lack of Prn production. Such mutations may lead to new, more effective vaccine components.

### 6.2.5 International developments

Maternal immunisation has been implemented in United Kingdom since 2012 and in Belgium (Flanders) since 2014. UK data show a good safety profile with no specific adverse outcomes observed and vaccine effectiveness estimates of 91-93% [5-7]. Preliminary data, presented at the EUPert-strain meeting in June 2015, point towards a possible small interference with infant primary series for diphtheria and Pertactin, assessed at 5 months of age. Hardy et al. also reported interference in infants whose mothers received a Tdap vaccine during pregnancy after the primary series, which was restored after a booster dose [8].

#### *6.2.5.1 Cost-effectiveness*

Thampi et al. assessed the cost-effectiveness of post-exposure prophylaxis (PEP) strategies for household contacts of pertussis cases in Canada [9]. Using a Markov model, 4 mutually exclusive strategies were examined: erythromycin, azithromycin, clarithromycin, or no intervention, stratified by age group of contacts ('infant', 'child', and 'adult'). Azithromycin offered the highest quality-adjusted life years (QALYs) in all scenarios. While this was the dominant strategy among infants, it produced an incremental cost-effectiveness ratio (ICER) of $ 16,963 per QALY among children and $ 2,415 per QALY among adults. The authors concluded that pertussis PEP is a cost-effective strategy compared with no intervention and plays an important role in contact management, potentially in outbreak situations. Azithromycin, which is generally the recommended drug in Dutch guidelines, proved to be the optimal strategy among all contact groups. In the Netherlands, pertussis PEP for all household members is recommended when unvaccinated or incompletely vaccinated infants or a woman in the third trimester of pregnancy is part of the household.

Fernandez-Cano et al. performed a cost-benefit analysis of two strategies for pertussis prevention in infants: a cocoon vaccination strategy and the vaccination of pregnant women versus the current vaccination policy in Spain [10]. The number of parents needed to vaccinate with the cocoon strategy to prevent 1 pertussis hospitalisation would be 4,752 and to prevent 1 death, more than 900,000. 1,331 pregnant women would have to be vaccinated to prevent 1 hospitalisation and 200,000 to prevent 1 death. The benefit-to-cost ratio (the ratio of the benefits of the strategy, relative to its costs) was 0.04 for cocooning and 0.15 for vaccinating pregnant women. In the situation in Spain, the strategy of vaccinating pregnant women would be the most favourable option.

### 6.2.6 Tables and figures

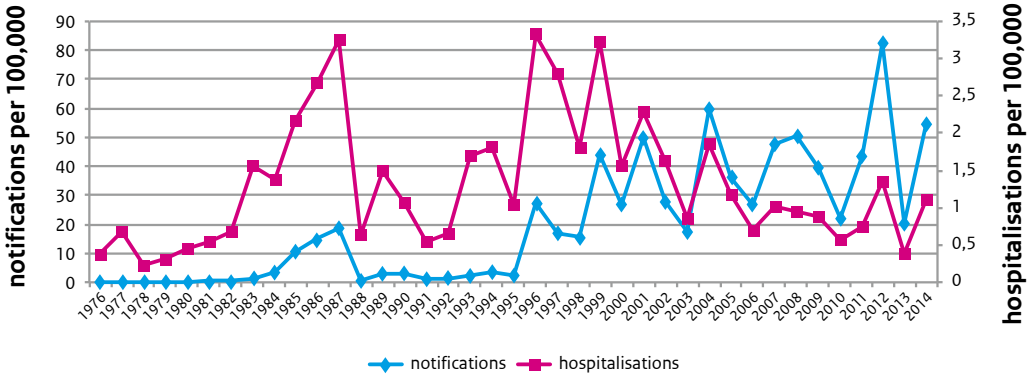


**Figure 6.2.1** Pertussis notifications (left Y-axis) and hospitalisations (right Y-axis) per 100,000 for 1976-2014

Note: For 2014, the hospitalisation data are preliminary and incomplete.

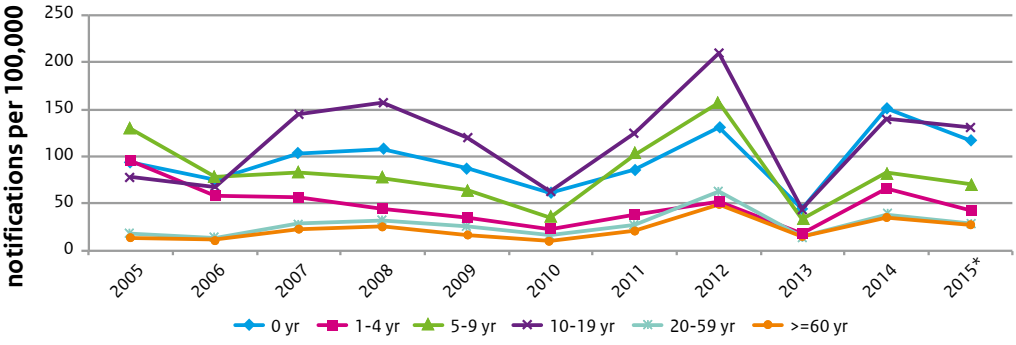


**Figure 6.2.2** Pertussis notifications per 100,000 per age category for 2005-2015

* For 2015, only notification with a first day of symptoms in the first quarter were included.

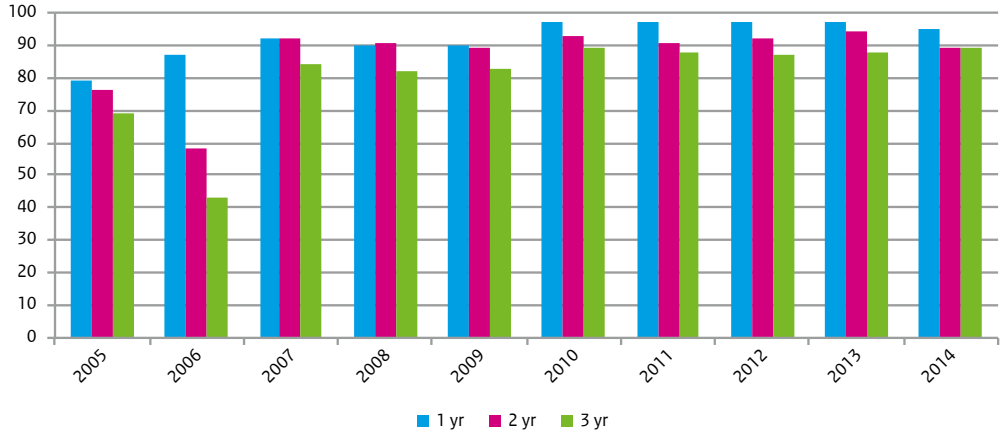


**Figure 6.2.3** Vaccine effectiveness (VE) for pertussis estimated for 1, 2 and 3 year-olds for 2005-2014 by the 'screening method'

**Table 6.2.1** Estimates of vaccine effectiveness (VE) for pertussis 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 | 16y |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1998** | | 74 | 68 | 77 | 73 | 60 | - | 45 | - | 18 | - | - |
| **1999** | 77 | 70 | 71 | 75 | 63 | - | 11 | 3 | - | - | - | |
| **2000** | 71 | 80 | 68 | 56 | 36 | 13 | - | 14 | - | 15 | | |
| **2001** | 82 | 79 | 71 | 47 | 49 | 24 | 5 | - | - | | | |
| **2002** | 86 | 71 | 51 | 35 | 34 | 59 | - | 27 | | | | |
| **2003** | 80 | 61 | 61 | 72 | 69 | - | 63 | | | | | |
| **2004** | 84 | 89 | 67 | 80 | 82 | 64 | | | | | | |
| **2005** | 83 | 87 | 86 | 93 | 67 | | | | | | | |
| **2006** | 93 | 90 | 82 | 81 | | | | | | | | |
| **2007** | 89 | 86 | 79 | | | | | | | | | |
| **2008** | 85 | 87 | | | | | | | | | | |
| **2009** | 92 | | | | | | | | | | | |

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

### 6.2.7 Literature


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* RIVM publication

## 6.3 Tetanus

*N.A.T. van der Maas, A.W.M. Suijkerbuijk, R. Donken, D.W. Notermans, H.E. de Melker*

### 6.3.1 Key points

- In the calendar year 2014 (n=0) and in 2015 (n=1) up to week 24, one case of tetanus was reported.
- A bedside test for tetanus immunity could be helpful in the decision on tetanus post-exposure prophylaxis.

### 6.3.2 Epidemiology

In 2014 and in 2015 up to week 24, one case of tetanus was notified in an 18-year-old unvaccinated male (Figure 6.3.1).

### 6.3.3 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.

### 6.3.4 Research

In the Netherlands, the number of tetanus cases reported each year is nearly always low.
A study into the use of tetanus post-exposure prophylaxis (T-PEP) guidelines by emergency departments (EDs) and general practitioners in the Netherlands demonstrated that the Health Council (HC) guideline on T-PEP is not always followed properly, resulting in over-immunisation and under-immunisation [1]. A study into the added value of a bedside test for tetanus immunity, the Tétanos Quick Stick® (TQS), among three EDs in the Netherlands showed that 22% of people who were born before the introduction of vaccination against tetanus in the NIP were not eligible for T-PEP according to the HC-guideline because they had a negative TQS (cut-off for positivity was 0.1 IU/ml), whereas this percentage was 8% amongst people born after NIP-start. These groups had low antibody titres and are probably not protected against tetanus. In contrast, 65% and 58% of the respective cohorts were eligible for T-PEP according to the HC-guideline but had a positive TQS, i.e. an antibody concentration above the protective level. Stricter adherence to the HC-guideline on T-PEP can prevent over-immunisation and decrease the risk of tetanus. Furthermore, the use of TQS would allow better targeting of T-PEP (van der Maas et al. submitted). Further research on the cost-effectiveness and the extension of the interval between consecutive tetanus toxoid (TT) booster doses in the Netherlands is necessary.

### 6.3.5 International developments

N'Diaye et al. evaluated the cost-effectiveness of using the TQS, a test for tetanus immunity screening for wounded patients in French emergency departments [2]. Two strategies were compared: a diagnosis of tetanus immunity by 'TQS' and a 'Medical Interview' (current practice). The outcome measures were the number of tetanus cases, life years gained and the costs from a

societal perspective. The use of TQS proved to be as effective in the number of life years gained and less costly than 'Medical Interview' when applied in an emergency department to wounded patients with tetanus-prone wounds or aged ≥65 years. However, the use of TQS was more expensive compared with current practice involving patients with non-tetanus-prone wounds.

### 6.3.6 Tables and Figures

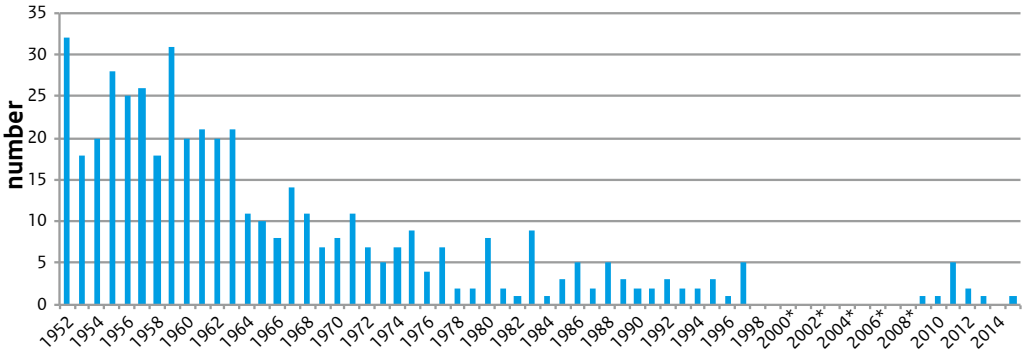


**Figure 6.3.1** Tetanus notifications in the Netherlands by year, 1952-2015

Note: between 1999 and 2009, tetanus was not notifiable. For 2015 notifications up to week 24 were counted.

### 6.3.7 Literature


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## 6.4 Poliomyelitis

*E. Duizer, W. Luytjes, H.E. de Melker, N.A.T. van der Maas*

### 6.4.1 Key points

- In 2014 and 2015 up to week 24, no cases of poliomyelitis were reported in the Netherlands.
- The temporary measures regarding the vaccination of Syrian refugee children below 5 years of age and intensified environmental surveillance that started in November 2013 at the first refugee entry point in the Netherlands were stopped as of April 2015. During this period, at least 1,283 children were vaccinated and 186 sewage samples were analysed. One poliovirus strain was found in a sewage sample collected at this refugee entry point: a Sabin 1 vaccine strain.
- Through routine enterovirus-surveillance, in July 2015 a VDPV type 3 was found in a young Syrian refugee. He had no clinical symptoms of polio. Follow-up of the case and surrounding contacts revealed no circulation of poliovirus.
- In the three polio-endemic countries (Afghanistan, Pakistan and Nigeria), reports on wild poliovirus type 3 have decreased substantially; In Nigeria, no cases of wild poliovirus have been reported since July 2014 to date.
- The WHO global action plan to minimize poliovirus facility-associated risk (GAPIII) was adopted at the 68th World Health Assembly, 18–26 May 2015. GAPIII aligns the safe handling and containment of poliovirus infectious and potentially infectious materials with the WHO Endgame plans.

### 6.4.2 Epidemiology

In 2014 and 2015 up to week 24, no cases of poliomyelitis were reported in the Netherlands (Figure 6.4.1).

#### *6.4.2.1 Global situation*

In 2014-2015, polio remained endemic in three countries – Afghanistan, Nigeria and Pakistan. In all three countries, a decrease in polio reports has been observed in 2015 relative to 2014. In Nigeria, no wild polio cases have been reported since July 2014 to date. In 2015 up to week 24, no importation of polio in non-endemic countries was observed.
Of the three strains of wild poliovirus (type 1, 2 and 3), wild poliovirus type 2 was eradicated in 1999. No wild poliovirus type 3 cases have been reported in 2015 up to June. Case numbers of wild poliovirus type 1 are at the lowest level ever and circulate in Pakistan and Afghanistan only. No circulating vaccine derived poliovirus has been reported in 2015 up to June. In March 2014, the WHO South-East Asia Region, including India, was certified polio-free.

### 6.4.3 Pathogen

In 2014, no wild poliovirus was found during the routine surveillance activities in the Netherlands. In one sample collected on January 29th, 2015 at the first refugee entry point in Ter Apel, the Netherlands, a Sabin vaccine strain poliovirus type 1 was found. Furthermore, through routine enterovirus-surveillance, a VDPV type3 was found in a young Syrian refugee in July 2015. He had no clinical symptoms of polio. A follow-up of the case and surrounding contacts revealed no circulation of poliovirus.
Worldwide, vaccine-derived polioviruses (VDPVs) can still be found, mostly in immunocompromised children (iVDPV). In 2014, 55 cases of VDPV (all but one type 2) were reported, in contrast with zero VDPV cases in 2015, up to week 24.

### 6.4.4 Current/ongoing research

In 2015, the environmental surveillance performed in the Netherlands will be optimised and revalidated. We are developing poliovirus-specific molecular detection protocols to be included in the enterovirus detection workflow in the Laboratories of Medical Microbiology (MML) to allow for timely poliovirus exclusion in enterovirus positive samples.
An Indian study into the efficacy of an inactivated poliovirus vaccine showed that inactivated polio vaccine (IPV) compared with vaccination with exclusively oral polio vaccine (OPV) reduced excretion for poliovirus types 1 and 3 between 38.9 and 74.2% and 52.8 and 75.7%, respectively. Thus, IPV in OPV-vaccinated individuals boosts intestinal mucosal immunity [1].

### 6.4.5 International developments

To further support and maintain polio eradication, all countries must continue vaccination, with IPV replacing OPV. Furthermore, the WHO global action plan to minimize poliovirus facility-associated risk (GAPIII) was adopted at the 68th World Health Assembly, on 18–26 May 2015. GAPIII aligns the safe handling and containment of poliovirus infectious and potentially infectious materials with the WHO Endgame plans.

*GAPIII*

1. Describes timelines and requirements to be completed in preparation for poliovirus type 2 containment implemented throughout the poliovirus type 2 containment period and applied in the post-eradication and post-bivalent OPV (bOPV) phase;
2. Addresses type-specific containment of wild poliovirus (WPV) as well as OPV/Sabin polio vaccine viruses, consistent with the goal of sequential cessation of OPV use after type-specific WPV eradication;
3. Balances the need for equitable access to polioviruses, e.g. for vaccine production, throughout the Poliovirus type 2 containment and post-eradication period, against the risk based on assessment findings, consequence models and management strategies; and
4. Establishes the long-term goal of minimizing the risk of facility-associated poliomyelitis in the post-eradication/post-bOPV era by providing continued access to safe and affordable IPV or Sabin-IPV and by reducing the number of facilities handling and storing polioviruses to a minimum while serving essential functions and meeting all required safeguards.

## 6.4.6 Tables and Figures

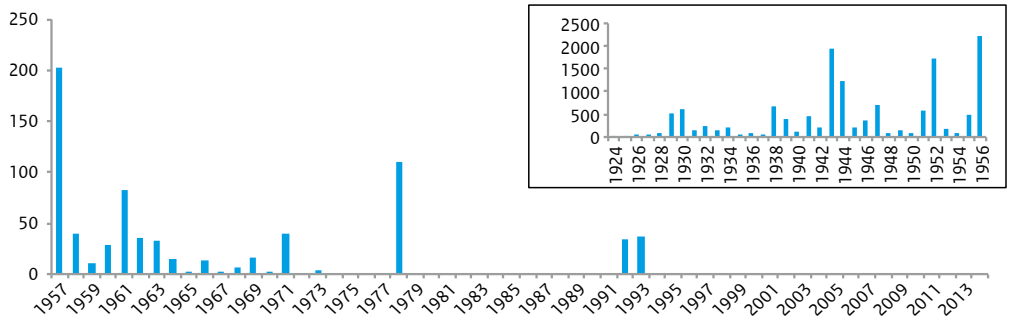
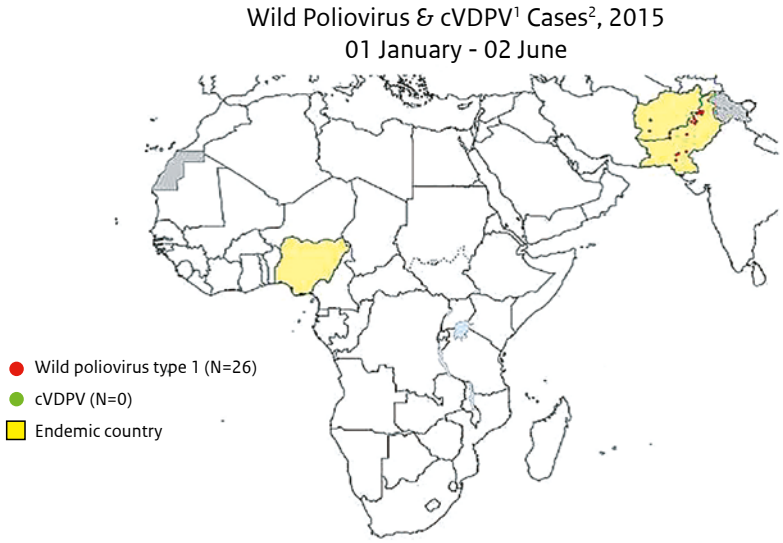



**Figure 6.4.1** Notifications of poliomyelitis in the Netherlands from 1924-1956 and 1957-2014




1 cVDPV is associated with ≥ 2 AFP casese or non-household contacts. VDPV2 cases with ≥ 6 (≥ 10 for type 1) nucleotides difference from Sabin in VP1 are reported here.
2 Excludes viruses detected from environmental surveillance.
Data in WHO HQ as of 02 June 2015

**Figure 6.4.2** Wild poliovirus cases worldwide

## 6.4.7 Literature

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

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### 6.5.1 Key points

- The total number of invasive disease cases caused by *Haemophilus influenzae* serotype b (Hib) in 2014 (n=29) was the same as in the previous year. The incidence among 0-4 year-olds decreased from 1.43 per 100,000 (n=13) in 2013 to 0.89 per 100,000 in 2014 (n=8), whereas in the other age-groups, except for 65 years and older, the incidence increased slightly.
- Since 2006 (n=14), the number of vaccine failures of invasive Hib disease decreased to an average of 7 vaccine failures per year with a range of 4 to 9 vaccine failures per year.
- Since 2004, there has been a steady increase in the number of cases caused by nontypeable Hi strains (NTHi) (71 in 2004 to 117 in 2014).

### 6.5.2 Epidemiology

#### *6.5.2.1 Hib disease*

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 and 37 cases. In 2014, the number of cases was 29 and in 2015 up to June, the number of cases was 13 (Figure 6.5.1). The incidence is highest among 0-4 year-olds and the elderly aged 65 years and older (Figure 6.5.2). The incidence among 0-4 year-olds decreased from 1.43 per 100,000 (n=13) in 2013 to 0.89 per 100,000 (n=8) in 2014, whereas in the other age-groups the incidence increased somewhat (from 0.05 per 100,000 (n=7) in 2013 to 0.1 per 100,000 (n=13) in 2014), except for people 65 and older (from 0.32 per 100,000 (n=9) in 2013 to 0.27 per 100,000 (n=8) in 2014).

#### *6.5.2.2 Nontypeable (unencapsulated) Hi (NTHi) strains*

The number of cases caused by NTHi increased from 30 in 1993 to 90 in 2003, partially because the number of blood isolates submitted for serotyping increased. Thereafter, it decreased again to 71 in 2004. From 2004 to 2014, a gradual increase in the number of cases from 71 to 117 was observed (Figure 6.5.1). In 2015, up to June, 80 NTHi cases were reported. In 2014, the highest incidence of NTHi was among the elderly aged 65 and older (2.06 per 100,000 (n=60)).

#### *6.5.2.3 Hif and other Hi serotypes*

In 2014, two cases of Hia, one case of Hid, three cases of Hie and 8 cases of Hif were reported. In 2015, up to June, one case of Hia, 4 cases of Hie and 7 cases of Hif were reported.

#### *6.5.2.4 Vaccine failures*

In the cohorts eligible for vaccination, the number of infections due to Hib showed a peak in 2005 (n=29), after which the number decreased until 2011 (n=7). Thereafter, it increased again (n=14 in 2013) and in 2014 the number of cases was at the same level as in 2012 (n=11). The number of vaccine failures showed a similar distribution (n=17 in 2005 and n=4 in 2011), except for the decrease in 2013 (n=6). In 2014, the number of vaccine failures was 7 and in 2015, up to June, the number of vaccine failures was 2. For 8 of the 9 vaccine failures in 2014 and 2015, up to June, it was known that they had no underlying disease. Five vaccine failures were in people under the age of five years and three were above that age.

### 6.5.3 Pathogen

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

### 6.5.4 International developments

Townsend et al. [1] performed a study to modify and optimise a serum bactericidal antibody (SBA) assay in order to evaluate the functional activity of Hib antibodies generated following Hib conjugate vaccination. The predictive protective SBA titre corresponding to a post-booster anti-PRP (polyribosyl-ribitol-phosphate) IgG of 1.0 μg/ml (long-term protective threshold derived by passive immunisation or immunisation with pure polysaccharide) was 8. The optimised SBA assay seemed to be specific and reproducible and correlated with anti-PRP IgG.

In England and Wales, the incidence of laboratory-confirmed neonatal invasive NTHi disease ranges between 2.1 and 4.8 cases per 100,000 live births, with nearly all infections occurring around the time of birth. Collins et al. [2] obtained detailed clinical information from all laboratory-confirmed cases in infants ≤ 31 days during 2009-2013 (n=118, of which 115 were NTHi). They found that early-onset neonatal NTHi disease was strongly associated with premature birth and caused significant morbidity and mortality.

An open-label, randomised, controlled study was performed whereby eligible healthy infants 6-12 weeks of age were randomly assigned in a 1:1 ratio to two vaccination groups: consistent limb (DTaP-IPV-Hib at 2, 3 and 4 months of age and PCV13 at 2, 4 and 12 months all administered to the right leg) or alternating limb (DTaP-IPV-Hib in the left leg at 2 months and in the right leg at 3 and 4 months and PCV13 in the left leg at 2 months, in the right leg at 4 months and in the left arm at 12 months). All infants in both groups received Hib-MenC-TT administered in the left leg at 12 months. Results showed that anti-PRP geometric mean IgG concentrations (GMCs) were lower in the consistent limb group than in the alternating limb group at 5 months and at 12 months, and anti-TT antibody IgG GMCs were also lower in the consistent limb group compared with the alternating limb group at 13 months and 24 months. Anti-pneumococcal IgG GMCs were similar between both groups at all-time points [3]. For the safety results found in this study, see Chapter 5.

## 6.5.5 Tables and Figures

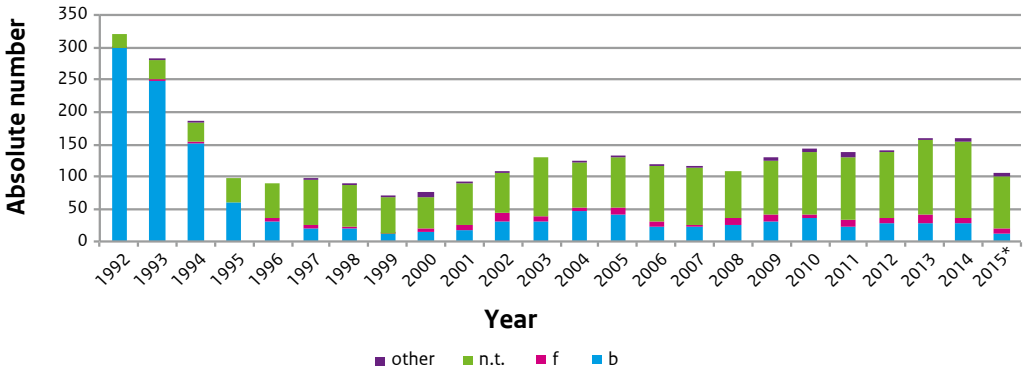


**Figure 6.5.1** Absolute number of *Haemophilus influenzae* isolates per serotype, 1992-2015* (* up to June)

Source: NRBM

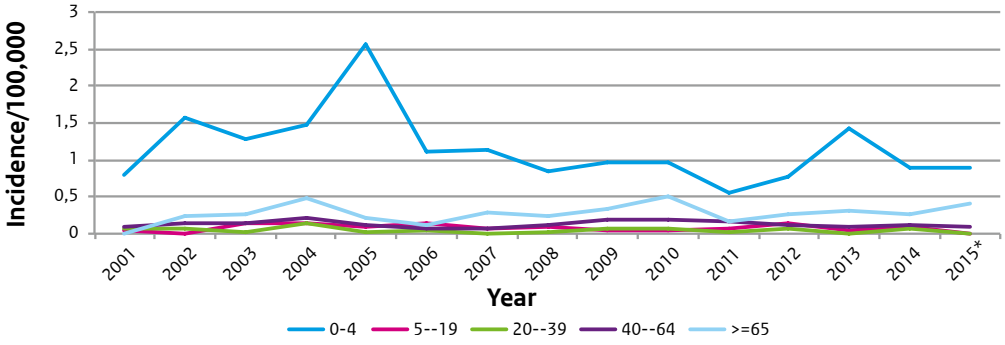


**Figure 6.5.2** Age-specific incidence of invasive *Haemophilus influenzae* type b (Hib) disease according to isolates, 2001-2015* (*up to June)

Source: NRBM

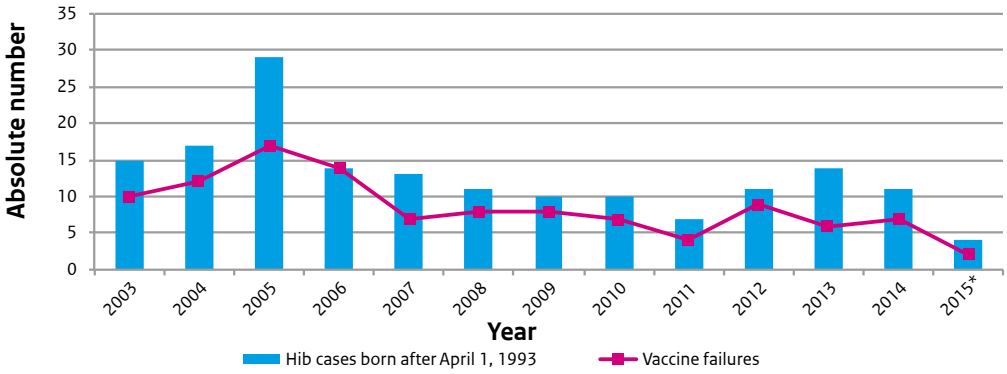


**Figure 6.5.3** Annual number of *Haemophilus influenzae* type b (Hib) disease in people eligible for vaccination (i.e. born after April 1, 1993) and the number of vaccine failures, 2003-2015* (*up to June)

Source: NRBM

### 6.5.6 Literature


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## 6.6 Mumps

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### 6.6.1 Key points

- The number of reports of mumps (n=40) in 2014 was low.
- In the first five months of 2015, indications of a mumps resurgence and endemic transmission were encountered.
- Most of the mumps cases in the Netherlands were caused by genotype G.

### 6.6.2 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. The first signs of an increase were observed in 2004 with an outbreak among (mainly vaccinated) students [1]. Subsequently, an outbreak occurred among unvaccinated schoolchildren in the Bible Belt (2007-2009) [2]. From 2009 onwards, a countrywide epidemic occurred that again particularly affected (vaccinated) student populations, with three epidemic seasons/peaks occurring up to the end of 2012 (n=1850; Figure 6.6.1) [3]. 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. In 2013, two outbreaks were identified in the north-west of the Netherlands ('Noord-Holland'), whereas the remaining cases were spread throughout the country.

In 2014, only 40 mumps cases were reported. Most of these cases were sporadic mumps cases or small clusters, which did not cause major outbreaks. This was also confirmed by genotyping the laboratory confirmed cases, because a high genotypic diversity was found among the cases tested. Fifty-three per cent were in males, the median age was 27 years (range 7-52). Sixty per cent were twice vaccinated, 8% once vaccinated and the vaccination status of 33% was unknown. Twenty-three per cent were students. One case was hospitalised, three cases were reported to have complications.

In 2015, until the 31$^{st}$ of May, 43 mumps cases were reported (Figure 6.6.1). Sixty-three per cent were males, the mean age was 23 (range 12-43). Sixty-five per cent were twice vaccinated. Thirty-three per cent were University or higher vocational education (HBO) students and 21% were intermediate vocational education (MBO) students. So far, two outbreak clusters have been identified. The first cluster is at a hockey club in the west of the Netherlands ('Zuid-Holland') and involves 11 reported mumps cases. The second cluster is linked to a pub and MBO college in the same area and involves 6 cases.

### 6.6.3 Pathogen

Since the mumps outbreaks in 2009, the mumps virus genotype that causes most of the mumps cases in the Netherlands is genotype G. Besides genotyping based on the mumps virus small hydrophobic (SH) gene, we have expanded the typing tools for mumps virus and sequenced the haemagglutinin-neuraminidase (HN) gene and fusion (F) gene of a subset of samples. Contrary to the SH gene sequence, which only shows minor variation within genotype G, the nucleotide variation in the HN gene and F gene sequences is more divergent and enables the investigation of transmission pathways. Based on this new molecular tool, we were able to link the second outbreak cluster in 2015 to the first cluster, indicating a resurgence of mumps and an endemic transmission of the mumps virus between March and May 2015.

### 6.6.4 Research

#### *6.6.4.1 Immunity in vaccinated persons*

In 2014, data from a serological study carried out among mumps-exposed students were published, showing that no clear cut-off of immune protection could be established based on mumps-specific IgG concentrations. However, pre-outbreak IgG concentrations were generally lower in infected persons than they were in non-infected persons [4].
Data on the dynamics and functionality of mumps-specific antibody levels during a mumps epidemic were published in 2015 [5]. Blood samples were obtained longitudinally from 23 clinically confirmed mumps cases, with or without a prior history of vaccination, and from 20 healthy persons with no serological evidence of recent mumps virus infection. Mumps patients had significantly higher mumps-specific IgG geometric mean concentrations compared with healthy controls 1-2 and 7-10 months post-diagnosis. Moreover, previously vaccinated mumps patients had significantly higher mumps-specific IgG and neutralizing antibody concentrations compared with unvaccinated mumps patients. IgG and neutralizing antibody concentrations declined significantly between 1-2 and 7-10 months post-mumps-diagnosis in vaccinated patients, whereas in non-vaccinated mumps patients concentrations where not significantly different at both time points. Other immunological mechanisms, including T-cell responses and neutralizing antibodies, are studied to investigate their contribution to immunological protection in vaccinated persons.

#### *6.6.4.2 Severity of mumps disease and viral shedding*

Twice MMR-vaccinated mumps patients have complications such as orchitis less often than unvaccinated patients. Furthermore, those people have mumps virus shedding in urine, which is a marker for a systemic mumps virus infection, less often. These findings indicate that, although the vaccine does not protect against mumps virus infection, MMR vaccination provides clinical protection to some extent.

#### *6.6.4.3 Genetic variability of mumps genotype G, the most prevalent genotype in mumps outbreaks*

All significant mumps outbreaks since 2010, including the new 2015 outbreak, were caused by genotype G wild type mumps virus. The genotype classification is based on sequence analysis of the SH gene. However, molecular resolution of the SH gene, though internationally acknowledged as the first genotype standard for mumps, proved too small to detect a new introduction of G type mumps viruses in the population and, consequently, too small to detect ongoing virus transmission. Now that we have expanded our genetic analysis to other structural mumps genes, we have discovered a genetic variability which has increased our capabilities to detect virus importation and virus transmission. Further research into this genetic variability and extending the data input by whole genome sequencing is ongoing.

### 6.6.5 International developments

In many countries around the world, mumps outbreaks have occurred in recent years [6-19]. Jin et al. summarised the geographic and chronologic distributions of 12 mumps genotypes [20]. In the Western Hemisphere, genotypes C, G, H, J and K were observed.
Several countries in Europe, including Finland and Belgium, have increased their research activities on the molecular, virological and immunological background of mumps vaccine failure. A collaborative effort between colleagues from the Belgian Scientific Institute of Public Health (WIV), Erasmus Medical Centre and the Centre for Infectious Disease Research, Diagnostics and Screening of the RIVM (RIVM/IDS) on epitope mapping has been initiated in 2015.

Different studies on seroprevalence, carried out in different countries where mumps vaccination was introduced in the past, have shown a seroprevalence above 80% in different populations [21-23].
During an outbreak of mumps in a high school in Spain, a reduced vaccine effectiveness following one dose of mumps vaccine was found [24]. Fiebelkorn et al. found modest increased mumps virus neutralising antibodies one month and one year after a third MMR dose, which could decrease human susceptibility during an outbreak [25].

### 6.6.6 Tables and Figures

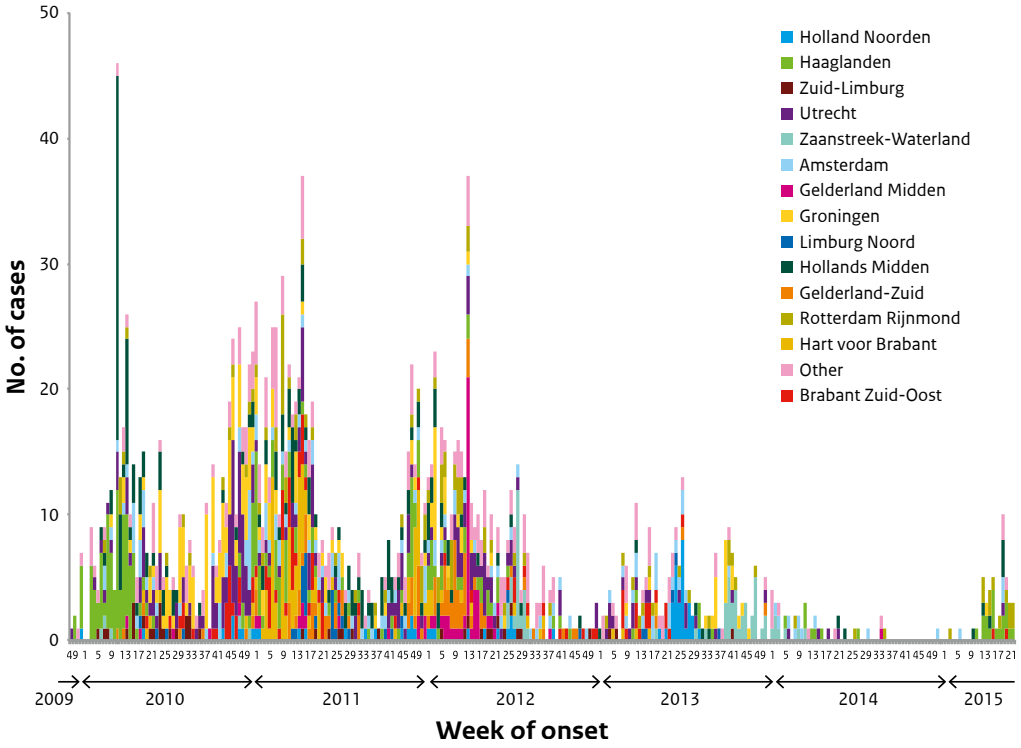


**Figure 6.6.1** Number of notified mumps cases by week of onset, 01/12/2009 -31/05/2015 (n=1855)

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* RIVM publication

## 6.7 Measles

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### 6.7.1 Key points

- In the epidemic that occurred in the Bible Belt in 2013-2014, 2,700 cases were reported. After correcting for under-reporting (9% reported), an estimated number of 30,000 measles infections occurred during this epidemic.
- In total, 140 cases were reported in 2014. The majority of the cases reported from January to March were part of the epidemic in the Bible Belt in 2013-2014. As a result of importations of measles cases, several other clusters emerged in the course of 2014.
- A 17-year-old was diagnosed with subacute sclerosing panencephalitis (SSPE). This SSPE patient had a history of having had measles at 4 years of age, during the 1999-2000 epidemic. Four months following the diagnosis of SSPE, the patient died.
- Measles research activities in 2014 have been focused on themes and questions formulated in different projects that largely have emerged because of the measles epidemic in 2013-2014. Most projects are still ongoing.

### 6.7.2 Epidemiology

In 2014, 140 measles cases were reported in the Netherlands (Figure 6.7.1). In January and February 2014, most reported measles cases were related to the epidemic in the Bible Belt, which began in May 2013 [1]. The genotype in this epidemic was D8 and the last reported case was on 12 March 2014. This epidemic comprised of 2,700 reported cases.

Although the epidemic ended at the end of February 2014, other clusters of measles cases occurred throughout the Netherlands because of importations (Figure 6.7.2). These importations could be discriminated based on (molecular) epidemiology. Two measles clusters, caused by different strains of genotype B3, occurred at Amsterdam Schiphol Airport in January – April 2014 (eight cases). These cases were linked to the measles outbreak that was ongoing in the Philippines. Additional clusters occurred in the province of Zuid-Holland in March-May 2014. The first cluster occurred among unvaccinated young infants in a day care centre (nine cases), a second among unvaccinated young infants at a day care centre social event (six cases but samples were not typed) and a third involved health care workers in a hospital (eight cases). The source of these clusters remains unknown but, based on genotyping results, a possible link with the first measles clusters around Amsterdam Schiphol Airport cannot be excluded. Lastly, two clusters of measles were independently reported in March and May 2014 in Zuid-Holland and Limburg. The sources of both importations were reported as coming from India (genotype D8).

Most of the 140 reported cases were male patients (60%). Most cases were unvaccinated (69%), 36 (26%) had received at least one MMR vaccination, and the vaccination status was unknown for 7 (5%) reported cases. Of the vaccinated cases, 19 (53%) had been vaccinated

once, 16 (44%) had been vaccinated twice and one (3%) had been vaccinated three times. The last measles case in 2014 was reported in September. Since then, no cases have been reported up to June 2015.

#### *6.7.2.1 Subacute sclerosing panencephalitis (SSPE)*

In 2014, a 17-year-old male was diagnosed with SSPE [2]. SSPE is a progressive neurological disorder, which presents itself after a latency period of the virus from an acute measles infection. The SSPE case had had measles at the age of 4 during the 1999-2000 measles epidemic in the Netherlands. Four months following the diagnosis of SSPE, the patient died.

### 6.7.3 Pathogen

The measles epidemic in the Bible Belt in 2013-2014 was caused by the 'Taunton' genotype D8, which was the most prevalent genotype in Europe in 2013. Most cases reported between January and March 2014 were still epidemiologically linked to this outbreak and were genetically identified as D8.

Between January and March 2014, two variants of genotype B3 (Harare, Tonbridge) were identified at Amsterdam Schiphol Airport, which involved partially vaccinated and unvaccinated adults. These cases pointed to two separate measles virus importation events related to air travel [3]. While the Harare variant of genotype B3 and genotype D8 were the major genotypes reported in most European countries in 2014, it is the Tonbridge variant of B3 measles virus that was subsequently identified among an outbreak of measles cases among young unvaccinated infants and health care workers in the region of Zuid-Holland in March and April. This outbreak resulted in secondary and tertiary measles transmission. While a direct relationship between this outbreak and the measles cluster around Amsterdam Schiphol Airport is lacking, the sequence identity suggests there is a possible link between both events.

### 6.7.4 Research

Measles research activities in 2014 have been focused on themes and questions formulated in different projects that largely have emerged because of the measles epidemic in 2013-2014. Most projects are still ongoing. (Preliminary) results, if available, will be discussed here.

#### *6.7.4.1 Evaluation of impact, coverage, tolerability and effects of early MMR vaccination*

During the epidemic of 2013-2014, infants between 6-14 months of age were offered an early MMR vaccination in municipalities with MMR1 vaccination coverage below 90% and/or when people belonged to an orthodox reformed family.

##### *6.7.4.1.1 Tolerability*

From preliminary results, it can be concluded that the early MMR vaccination given to infants between 6 to 14 months is well-tolerated. Parents of 59 (6.1%) and 350 (36.4%) infants reported local and systemic adverse events (AEs), respectively. Lower frequencies of systemic AEs were found in 6-8 month-old infants, compared with 9-11 and 12-14 month-old infants. Frequencies of local AEs were not significantly different among the different age categories. Consequently, measles vaccination is a safe intervention to protect young infants against measles.

#### 6.7.4.1.2 *Coverage*

A study was conducted in 2014 to assess the uptake of early MMR during the measles epidemic in 2013-2014 using vaccination records from 2003-2013 in Praeventis. Over 10,000 children were invited for an early MMR vaccination, 6,552 (65.9%) of which received vaccination.

#### 6.7.4.1.3 *Vaccine effectiveness (VE)*

Preliminary results from estimates of the VE of the early MMR vaccination suggest that vaccinated infants between 6 and 14 months old have a lower risk of contracting measles than unvaccinated infants. Vaccinated infants were 95% (95%CI: 80-98%) less likely to contract laboratory confirmed measles than unvaccinated infants. However, when adjusted for confounders related to measles exposure, this effect decreased to 73% and became insignificant (95%CI: 72-96%). Further investigation is needed into whether the effectiveness estimates reflect the protective effect of the vaccine or a difference in exposure between vaccinated and unvaccinated infants.

### 6.7.4.2 *Immune responses to MMR vaccination of infants between 6 and 14 months old (EMI study)*

This study was initiated during the measles epidemic in 2013-2014 and involves an observational study in young children who received an early measles immunisation between 6 and 12 months of age, as well as the regular MMR immunisation at 14 months of age. The aim of this study is to investigate humoral and cell-mediated immunity against measles following this early measles immunisation and to compare this with a control group of children receiving measles immunisation only at 14 months of age. Based on the knowledge from literature, it is anticipated that both the presence of maternal antibodies and early measles immunisation will significantly influence vaccine efficacy and immunological outcome. Secondary objectives include the moderating effect on the immunogenicity of other infant concomitant vaccines (DTaP-Hib-HepB, Pneumo, MenC) that are routinely administered to infants between 2 and 14 months of age as part of the Dutch NIP. The inclusion of the children is almost finalised.

### 6.7.4.3 *Under-reporting*

Measles is a notifiable disease but not all cases will consult their General Practitioner (GP), nor will all consultations be reported. The 2,700 cases of measles reported will therefore be an underestimation of the actual number of infections during the epidemic of 2013-2014. A survey was conducted to identify measles cases in persons up to 15 years old in a municipality with vaccination coverage of 80%. Self-identified cases were matched with the cases reported to the Dutch national surveillance system (Osiris) to estimate under-reporting. Nine per cent (95%CI: 6-12%) of the cases in the municipality where the study took place were reported. It can therefore be assumed that the number of measles infections was 11 times higher than the number of reported cases, so the actual number of infections during the epidemic of 2013-2014 in the Netherlands was approximately 30,000.

### 6.7.4.4 *Validity of measles antibody screening of personnel in the health care setting*

We re-evaluated different immunoassays for assessing measles immunity among HCW, including multiplexed immuno assays (MIA, based on Luminex technology) - that has been developed for population-based serosurveys at RIVM (e.g. PIENTER). We compared these

assays with the plaque-reduction neutralisation (PRN) test, the best surrogate marker for vaccine efficacy and immune protection, and recently adopted by WHO. Commercial enzyme immunoassays (EIAs) failed to detect measles IgG antibodies in at least 10% of the vaccines, while this percentage was approximately 3% for the MIA. Negative IgG results rose up to 20% for those born between 1975 and 1985, pointing to an age group largely representing vaccinated persons from the first measles vaccination period in the Netherlands. The results show limitations to the usefulness of current EIAs for determining protective measles antibodies in persons with a vaccination history, except for MIA developed by RIVM, which proved much better in this context. The results have been recently published [4].

#### *6.7.4.5 Measures taken by Dutch hospitals to prevent measles in health care personnel*

A cross-sectional online survey among Dutch hospitals has been conducted to examine which preventive measures, in addition to hygiene and isolation measures, were taken by Dutch hospitals in order to prevent measles in health care personnel. The majority of Dutch hospitals took additional measures to prevent measles in health care personnel during the measles epidemic in 2013-2014, such as assessing susceptibility to measles among health care personnel, offering vaccination to health care personnel that are susceptible to measles and implementing adequate post-exposure policies. Preliminary results show that hospitals that consist of a single location more often had sufficient preventive measures in place then did hospitals that consist of multiple locations. This suggests that the development of future guidelines for preventing infection in hospitals can be improved by considering hospital characteristics.

#### *6.7.4.6 Environmental surveillance for measles*

Sewage-environmental surveillance, specifically carried out to exclude the circulation of poliovirus, was temporarily adopted for measles during the measles epidemic in 2013 at locations where vaccination coverage for both polio and measles is relatively low (schools/ villages in the Bible Belt). This was carried out as a proof of principle to investigate the resolution of this type of viral surveillance, both for poliovirus and for outbreaks with other viral ethology (e.g. norovirus). The detection of measles RNA in environmental samples was indeed successful and it also matched the clinical and laboratory reporting of measles in a temporal/geographic manner. These results will be integrated into a combined report/ manuscript on measles and polio in 2015.

#### *6.7.4.7 Societal costs of the measles outbreak*

In addition to the burden of disease, measles outbreaks have an economic impact on a society. Assessing the costs of the outbreak of 2013-2014 can help with planning for future outbreaks and optimising the allocation of public health authorities. A recently performed study showed that the outbreak was associated with substantial costs amounting up to approximately € 3.9 million for 2,700 notified cases or € 1,741 per notified case. Outbreak management costs were the primary cost driver. This is probably due to demands for expert advice, extensive media attention, the registration of notified cases and additional surveillance activities. When taking the extent of under-reporting into account, the estimated costs of hospitalisations and consultations with the general practitioner would be approximately € 0.9 million higher [5].

#### *6.7.4.8 Effect of vaccination on complications and the transmission of measles*

The epidemic in the Netherlands provided an opportunity to investigate the effect of vaccination on the severity and transmission of the infection. We extracted information on vaccination status, complications (encephalitis, pneumonia and otitis media) and the most likely source(s) of infection from the national surveillance system (Osiris). A case was defined as having transmitted measles when it was listed as a likely source for at least one other case. We estimated the age-adjusted effect of vaccination on the outcomes, complications and transmission through logistic regression. Of 2,674 reported cases with known vaccination status and eligible for vaccination, 2,533 (94.7%) were unvaccinated, 125 (4.7%) had been vaccinated once and 16 (0.6%) had been vaccinated twice. Of all cases, 328 (13%) reported at least one complication, most often pneumonia (6%). Of the unvaccinated cases, 316 (13%) had at least one complication, compared with 12 (9%) vaccinated cases (OR 0.5 (95%CI 0.3-1)). None of the twice-vaccinated cases had complications. In total, 201 cases were indicated as a likely source. Of the unvaccinated cases, 194 (8%) were a likely source and seven (5%) of the vaccinated cases were (OR 0.7 (95%CI 0.3-1.5)). None of the twice-vaccinated cases was indicated as a likely source. Our findings suggest that vaccination has a protective effect on the occurrence of complications and transmission, and they support the WHO recommendation of a two-dose MMR vaccination schedule.

#### *6.7.4.9 The effect of school holidays on measles transmission*

The 2013-2014 epidemic occurred for a large part during the summer holidays, during which incidences decreased. As school closure is a public health measure often suggested for emerging infections, this observation provided an opportunity to obtain a good estimate of its effect. Preliminary results, based on subdividing the population into three regions based on the timing of the school holiday (South, Middle, North), suggest a total reduction in transmission of about 60% during the summer holidays. This would have prevented the measles epidemic if the virus had been introduced during summer. However, whereas 90% of all transmissions occurred locally during the school term, this declined to 20% during the holiday. This would suggest that school closure might increase the spread of infections across regions. At present, it is not yet clear if this is a specific summer effect (e.g. through summer camps) or whether this would also occur if schools were closed as a public health measure.

#### *6.7.4.10 Research projects related to WHO*

RIVM was chosen by the WHO to conduct a systematic review and critical appraisal of the evidence to ascertain whether the effect of a measles-containing vaccine (MCV) schedule that started younger than 9 months of age – in terms of immunogenicity, efficacy or effectiveness, the duration of protection and safety – is equal to or less than the effect of the current MCV1 recommended at 9-12 months. This review will serve as input for the Strategic Advisory Group of Experts (SAGE) on immunisation, currently planned for late October 2015.

The WHO and Centres for Disease Control and Prevention (CDC) acknowledged RIVM Luminex-based serology (MIA) for measles and rubella seroprevalence in 2014 and intends to share and build this capacity in the WHO measles and rubella laboratory network. The specific aims for 2015/2016 are to establish the MIA technique at CDC and validate the measles and rubella

serology, and to subsequently transfer the technology to regional laboratories within the WHO Laboratory Network. The first agreement was reached at the WHO Labnet Meeting in Geneva on July 1, 2015.

### 6.7.5 International developments

During 2014, 3,616 measles cases were reported by 30 EU/EEA countries. Most cases were reported by Germany and Italy (59%). The highest notification rates were among infants under one year of age (38.1 cases per million population). Of the cases with known vaccination status (n=3240), 83% were unvaccinated. Compared with previous years, the number of reported cases in Europe was low [6].

### 6.7.6 Tables and Figures

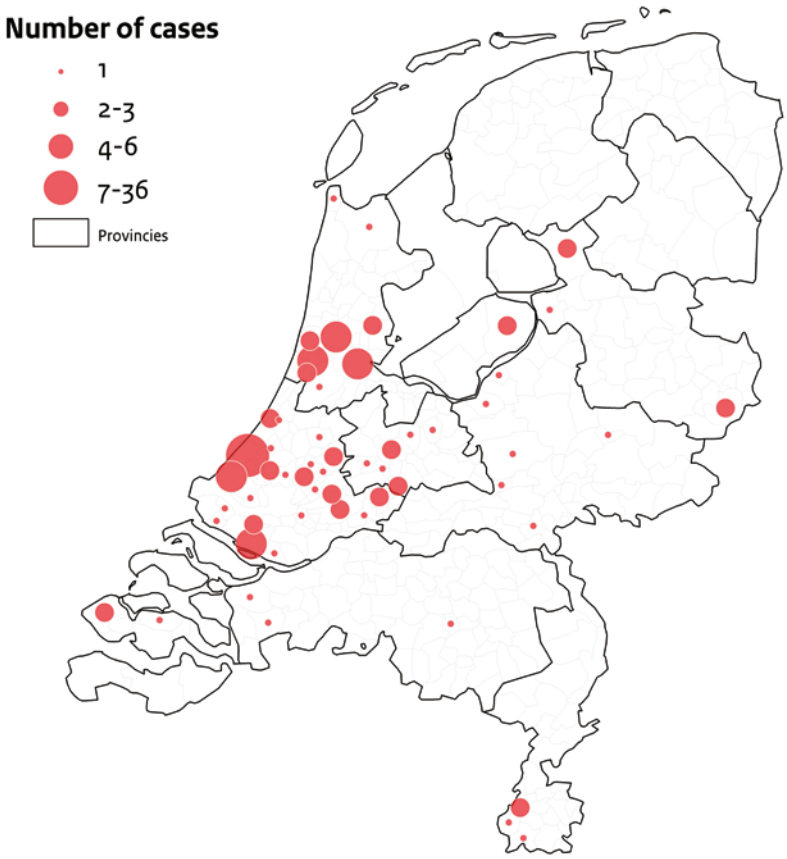


**Figure 6.7.1** Measles notifications by municipality from January 2014 to June 2015 (n=139, one missing)

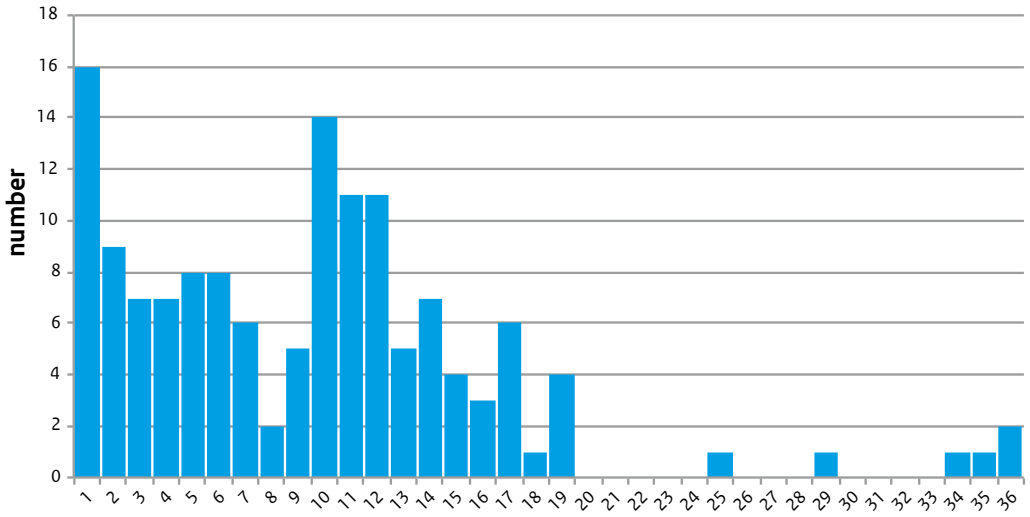


**Figure 6.7.2** Measles notifications by week of rash onset (n = 140), 1-1-2014 to 30-6-2015

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* RIVM publication

## 6.8 Rubella

*N.A.T. van der Maas, W.L.M. Ruijs, N.Y. Rots, R. van Binnendijk, S. Hahné*

### 6.8.1 Key points

- In the calendar year 2014 (n=2) and in 2015 up to week 25 (n=0), two rubella cases were reported. Those cases were not related.
- In 2013, a large rubella outbreak started in Poland. In 2014 and in 2015 up to week 25, this outbreak still continues, although reported numbers are decreasing.

### 6.8.2 Epidemiology

In the calendar year 2014 and in 2015 up to week 25, two rubella cases were reported. One case was an unvaccinated infant; the other was an unvaccinated male who contracted rubella in Indonesia.

### 6.8.3 Pathogen

The reported adult rubella case appeared to be infected with genotype 1E rubella virus and with a sequence type, which matches that of rubella viruses that were endemic in South-East Asia in 2014 and the epidemiological source (Indonesia). The source of infection in the infant case is unknown, the disease was confirmed by IgM serology; no genotyping results are available.

Genotype 2B, which is by far the most prevalent genotype reported in outbreaks on the European continent in recent years (according to genotype data extracted from the new WHO/HPA 'Rubens' genotype database.)

### 6.8.4 Research

A multidisciplinary Dutch expert group was convened to prepare a national guideline on rubella screening during pregnancy. In the Netherlands there is no uniform policy on rubella screening. Some midwives screen all pregnant women, some only risk groups and others do not screen at all. Given the high vaccination coverage and low incidence of rubella, screening of all pregnant women is not cost-effective [1]. Furthermore, there is increased discussion on the validity of rubella IgG tests to determine the immune status in vaccinated women, which needs to be further re-evaluated. The guideline is expected in 2015/2016.

### 6.8.5 International developments

In 2013, a large rubella outbreak started in Poland with more than 38,000 cases reported. The outbreak is ongoing, with over 4,500 cases reported in 2014 and 2015 up to June (*http://ecdc.europa.eu/en/healthtopics/rubella/epidemiological-data/pages/epidemiological_data.aspx*). The WHO initiated a rubella IgG standardisation workgroup in 2013/2014, as it turns out that many of the currently applied commercial tests for rubella IgG screening during pregnancy no longer meet the criteria for providing the immune status of rubella and also because many women currently gain this immunity from MMR immunisation and not from natural infection.

Follow-up studies and recommendations for the use of serological tests for rubella are expected to be presented by this international group in 2015/2016.

### 6.8.6 Literature

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* RIVM publication

## 6.9 Meningococcal serogroup C disease

*L. Mollema, H.E. de Melker, F.R.M. van der Klis, P. Kaaijk, N.Y. Rots, A. van der Ende, L. Spanjaard, S.P. Stoof, M.B. van Ravenhorst, E.A.M. Sanders, G.A.M. Berbers*

### 6.9.1 Key points

- In 2014, 3 cases of meningococcal group C (MenC) disease were reported and in 2015 (until June) 5 cases of MenC including one vaccine failure.
- In the UK, the adolescent MenC conjugate vaccine currently recommended for 13-14 year-olds will be replaced with the MenACWY conjugate vaccine in response to a continuous rise in cases of MenW since 2009.
- In May/June 2015 there was a small outbreak of serogroup C meningococcal disease among men who have sex with men (MSM) in the Chicago metropolitan area.
- In France the high serogroup C invasive meningococcal disease (IMD) incidence caused by C:P1.5-1,10-8:F3-6:cc11 isolates and the persistence of cases linked to the men who have sex with men (MSM) community led to the MenC vaccination recommendation targeting MSM and individuals aged 25 years and older attending social venues associated with the gay community.

### 6.9.2 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 from 1.38 per 100,000 in 2002 to 0.02 per 100,000 in 2014 (Figure 6.9.1). In 2014, 3 cases of invasive meningococcal group C disease were reported: one male from Poland who was 24 years old with unknown vaccination status and two unvaccinated females of ages 50 and 70 years. In 2015 up to June, 5 cases of invasive MenC disease were reported: four males aged 0, 22, 37 and 68 years and one female aged 75 years died due to the disease. It was unknown whether the 75-year-old female had an underlying disease. The male aged 22 years was vaccinated with NeisVac-C and therefore constitutes a case of vaccine failure. This is the fourth vaccine failure case to occur since the introduction of the conjugated MenC vaccine in 2002. Two of the patients involved in the vaccine failures were known to have had an immune deficiency.

### 6.9.3 Pathogen

See the first paragraph of Section 6.9.4.

### 6.9.4 Research

A retrospective study using Dutch surveillance data on IMD from June 1999-June 2011 was conducted to provide updated and representative information on the burden of IMD in the Netherlands and to assess the relationship between the clonal complex (CC) of the infecting strain and clinical manifestation, disease course and outcome [1]. Clinical information was retrieved from hospital records. Results showed that IMD mainly affects young and healthy individuals, most patients (48%) develop distinct meningitis and one-third of IMD patients

develop septic shock. The case-fatality rate (CFR) throughout the study was 8%, which was higher for adults than for children. Furthermore, this study showed that the disease course and outcome are mainly affected by age and clinical manifestation and much less by meningococcal clonal complex or serogroup. Underlying comorbidity, whether immunocompromising or not, has no effect on the disease course or outcome. Septic shock is the main determinant of the burden of IMD with higher percentages of intensive care unit (ICU) admittance, mortality and (severe) sequelae compared with meningitis or mild meningococcemia.
Information on CC was available for 900 patients and categorised into six groups based on the prevalence of the different CCs. Most prevalent was CC41/44 (47%), followed by CC32 (16%), CC11 (16%), CC213 (4%), CC269 (3%), with the remainder categorized as 'other CCs' (13%). CC11 was less prevalent among patients aged 0-4 years, compared with patients aged 10-64 years. The proportion of cases involving septic shock (with and without meningitis) did not differ between CCs. The CC of the infecting strain had no significant effect on CFR or the development of sequelae.

In a study by Stoof et al. [2], salivary antibody levels in adolescents were analysed in response to a meningococcal serogroup C conjugate booster vaccination nine years after priming in healthy 10, 12 and 15 year-olds. The parenteral MenC-TT booster vaccination induces a clear increase in salivary MenC-PS-specific IgG and IgA levels and the persistence of the highest levels correlates with age. Additionally, they showed that MenC-PS-specific IgG and IgA levels in saliva strongly correlate with the levels in serum. Therefore, saliva may offer an easy and reliable tool for future antibody surveillance.
Furthermore, preliminary results of the 3-year follow-up of this study indicate that, while a rapid decline of MenC-specific functional antibodies in serum was observed in the first year after the meningococcal conjugate C (MenCC) booster vaccination, a much slower decline was observed between the 1st and 3rd years.

For a comparison between the monovalent and tetravalent meningococcal booster vaccines, 410 healthy 10, 12 and 15 year-olds were enrolled between March and May 2014 and received a MenCC or a MenACWY conjugated vaccine 11 years after priming with MenCC vaccine. Blood and saliva samples were collected prior to vaccination, as well as 1 month and 1 year after booster vaccination. This study will provide important data for future considerations of a meningococcal booster vaccine in the Netherlands. Results are expected at the end of 2015.

In a nationwide surveillance study, MenC invasive disease between 1998 and the introduction of Meningococcal conjugate vaccines (MCC; 2002) was compared with the invasive MenC disease appearing from 2002 to 2012 in age groups eligible and not eligible for vaccination. In addition, the proportions of isolates from clonal complexes (ST-11 and ST-8) that are known to have a high expression rate of their polysaccharide capsule during nasopharyngeal carriage were compared between the pre-vaccination and post-vaccination periods. Results showed that there was a 99% decline in MenC disease in patients eligible for vaccination and a 93% decline in those not eligible. Furthermore, 36% of the overall MenC reduction had occurred in the unvaccinated population. The decline in MenC incidence was most pronounced among ST-11 and ST-8 complex serogroup C meningococci and therefore signalled a reduced carriage of these meningococci [3].

### 6.9.5 International developments

By the end of May 2015, 170 MenW cases had been reported in the UK in the epidemiological year 2014/2015, compared with 88 and 46 cases for the same period in 2013/2014 and 2012/2013, respectively. Because of the continuing rapid increase in MenW disease, the UK Departments of Health announced a rapid introduction of an adolescent MenACWY conjugate vaccine programme to begin in August 2015. The adolescent MenC conjugate vaccine currently recommended for 13-14 year-olds will be replaced by the MenACWY conjugate vaccine. Over the next two years, all remaining adolescents in the 13-18 year age groups will be offered MenACWY conjugate vaccine [4].

From May 12 to June 8, 2015, five cases of culture-confirmed serogroup C meningococcal disease among MSM were reported in the Chicago metropolitan area. Health care providers should consider the vaccination of at-risk MSM travelling to Chicago. Risk factors include MSM, HIV infection and the use of online 'hook-up' apps to meet anonymous sexual partners. Based on case demographics, African American MSM appear to be at increased risk. In anticipation of the 46th Annual Chicago Pride (June 20-21, 2015) and Chicago Black Pride (July 2-5, 2015) events, CDC recommends increasing awareness of the signs and symptoms of meningococcal disease among MSM and suggests considering the vaccination of individuals travelling to Chicago who are (1) sexually active MSM infected with HIV and (2) MSM who have sex with anonymous partners or use online 'hook-up' apps to identify male sexual partners.
In the Netherlands, the subtype (P1.5-1, 10-8, F3-6), which had caused several outbreaks among MSM in past years, has occurred only once since 2010 (in 2013) in an unvaccinated young girl. In the period 2004-2009, this subtype occurred 5 times among males 16 years and older. These 5 patients lived in different cities and the time interval between cases ranged from 6 weeks to 3 years [5]. Since January 2015, a question was added to the RIVM Osiris MenC questionnaire to discern whether the meningococcal case belongs to the MSM group. No cases belonging to MSM group were reported up to June 2015.
In France a national enhanced surveillance was established in response to the several outbreaks among MSM in past years in various countries. Since July 34 cases of serogroup C IMD have been notified in the Paris region. Of the 29 isolates, 14 were related to the genotype C:P1.5-1, 10-8:F3-6:cc11, of which nine isolates showed additional specific markers (similar to earlier outbreaks among MSM, such as in Germany). They corresponded to seven men (one aged 15-24 years and six aged 25-29 years) and two women (one aged 15-24 years and one in the age group 60 years and older). One additional male case (15-24 years-old) was epidemiologically linked to one of them (family cluster). These 10 cases were directly or indirectly linked to the MSM community, four cases of which, aged 25-29 years, self-identified as MSM. The four cases of serogroup C IMD among 25-29 year-old MSM (individuals older than 25 years are not targeted by the national vaccination programme) were 10 times greater than the expected number of men in this age group. In addition, the surveillance data highlighted that two family clusters of two cases each were also reported outside the Paris region in 2014, indicating that such isolates may spread all over the country and not only in the Paris region. Based on the above, the French public health authorities renewed the earlier recommendation of MenCC vaccination in November 2014 for one year and extended it beyond the Paris region to include the whole country, targeting MSM and all individuals aged

25 years and older attending social venues associated with the gay community. The observed increase in MenC IMD suggested a lack of vaccine-induced herd immunity caused by low vaccine uptake (56% at the age of two years and 17% among the 15 to 19 year-olds in 2013) [6].

Ishola et al. (2015) [7] had compared the immunogenicity and safety of either a CRM-conjugated or a TT-conjugated MenACWY vaccine in 93 teenagers (aged 16-19 years) who received either MCC-TT or MCC-CRM during a primary vaccination study 12-14 years earlier. A relatively greater proportion of those primed with MCC-TT had protective SBA titre, compared with the MCC-CRM primed groups. Post-boosting both MenACWY vaccines induces protective SBA titres to all 4 serogroups in most participants (98% at 1 month and ≥90% by 9 months post boost). The highest MenC SBA titres were seen in those MCC-TT primed and MenACWY-TT boosted, followed by those boosted with MenACWY-CRM, irrespective of priming, and then those MCC-CRM primed and MenACWY-TT-boosted.

### 6.9.6 Tables and Figures

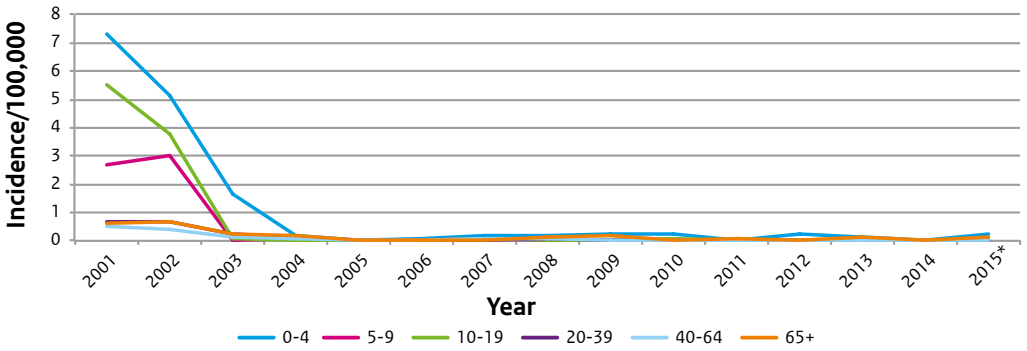


**Figure 6.9.1** Age-specific incidence of meningococcal C disease, 2001-2015 (*up to June)
Source: NRBM

**Table 6.9.1** Absolute numbers of invasive meningococcal C isolates, 2001-2015 (*up to June)
Source: NRBM

| Age in yrs | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **0-4** | 73 | 52 | 17 | 2 | 0 | 1 | 2 | 2 | 2 | 2 | 0 | 2 | 1 | 0 | 1 |
| **5-9** | 27 | 30 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **10-19** | 105 | 73 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| **20-39** | 31 | 32 | 12 | 6 | 1 | 1 | 1 | 3 | 2 | 2 | 1 | 0 | 1 | 1 | 2 |
| **40-64** | 27 | 20 | 7 | 4 | 2 | 1 | 5 | 3 | 1 | 0 | 0 | 1 | 0 | 1 | 0 |
| **65+** | 14 | 15 | 5 | 4 | 1 | 1 | 0 | 3 | 4 | 0 | 2 | 0 | 4 | 1 | 2 |
| **Total** | 277 | 222 | 42 | 17 | 4 | 4 | 10 | 11 | 9 | 6 | 3 | 3 | 6 | 3 | 5 |

### 6.9.7 Literature


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* RIVM publication

## 6.10 Hepatitis B

*S. Hofstraat, F. van Heiningen, B. van Benthem, I. Veldhuijzen, J. Cremer, K. Benschop, A.J. King, S. Hahné*

### 6.10.1 Key points

- The incidence of acute hepatitis B virus (HBV) notifications in 2014 was 0.8 per 100,000 of population, comparable to 2013.
- Among men, sexual contact with men remained the most frequently reported risk factor. For women, heterosexual contact was the most frequently reported risk factor.
- Molecular surveillance shows type A to be the dominant genotype among acute HBV cases, followed by type D.

### 6.10.2 Epidemiology

In 2014, 1,224 cases of HBV infection were notified. Of these, 1,074 (88%) were chronic infections and 141 (12%) acute infections (9 cases unknown status). Compared with 2013 (145 cases), the number of notified acute HBV infections decreased slightly. The incidence of acute HBV notifications in 2014 was 0.9 per 100,000 of population (2013: 0.8/100,000), 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 overall (Fig. 6.10.1). However, in the province of Friesland (Northern region of the Netherlands) a notable increase of acute HBV cases was found in 2014 (n=15), compared with 2013 (n=4). Similar clusters of acute cases in rural parts of the Netherlands have been identified by Soetens et al. [1] who described clusters of acute HBV cases in the south-western and north-eastern regions of the Netherlands in the period 2009-2013.
In 2014, most cases of acute HBV infection (57%) were acquired through sexual contact. For 31% of reports of acute HBV infection, the most likely route of transmission remained unknown, despite source tracing. Among men (104 cases), sexual contacts between men who have sex with men (MSM) accounted for 30% of acute infections and heterosexual transmission for 19%. Among women (37 cases), heterosexual contact accounted for 62% of the cases.

#### *6.10.2.1 Chronic HBV epidemiology*

Since 2009, the number of chronic HBV notifications has decreased by 41% (n=1820 in 2009 and n=1074 in 2014). The reason for this decline is unknown, but as chronic hepatitis B is largely asymptomatic, it is likely to reflect changing testing practices. In 2014, more than half of the cases (56%) acquired chronic HBV infection through vertical transmission. Six per cent were infected by sexual contact. For 28% of the reports of chronic HBV infection, the most likely route of transmission was unknown. For the remaining 10%, transmission occurred via injecting drug use (IDU), needle stick injuries or via other routes. Eighty-two per cent of the chronic HBV patients were born abroad (with Turkey, China, Ghana, Vietnam and Suriname as the five most frequently reported countries of birth).

### 6.10.3 Pathogen

Molecular sequencing and typing of 92 acute HBV cases (65%) was done in 2014. PCR amplification and sequencing gave results for 88 (96%) samples for the S-region. A minimum spanning tree based on S-region sequences is shown in Figure 6.10.2. This shows that the largest cluster of cases continues to be among genotype A cases, the most common genotype in the Netherlands.

#### *6.10.3.1 Molecular typing*

The molecular typing of notified acute HBV cases and of chronic HBV cases in the target groups for selective vaccination will continue in 2015. Besides molecular typing, molecular data can be used to analyse the circulation of genetic variants, such as possible immune escape variants and antiviral resistant variants [2], to assess the current vaccination campaigns and the impact of factors such as the influx of non-endemic strains and to gain insight into transmission networks in the Netherlands. For efficient analysis and surveillance of these variants, the Centre for Infectious Disease Control of the RIVM (RIVM/CIb) is working on implementing the molecular platform VIRO-TypeNed [3] of HBV, as well as the hepatitis C virus, of both acute and chronic cases. The platform aims to combine molecular data with epidemiological and transmission data to allow for a more efficient surveillance of HBV, source monitoring and detection of antiviral resistance and immune escape variants.

### 6.10.4 International developments

In March 2015, the WHO [4] issued its first hepatitis B guidelines: 'Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection'. It focuses on the care and treatment of persons living with chronic hepatitis B infection, as well as existing recommendations for the prevention of HBV. These include infant hepatitis B vaccination, catch-up vaccination and other prevention strategies for high-risk populations (MSM, commercial sex workers), as well as the prevention of transmission in health care settings.

Jazwa et al. [5] performed an economic analysis of an overseas hepatitis B programme for refugees. They carried out a cost-benefit analysis comparing two strategies among refugees from 82 countries of origin coming to the United States of America who were at an increased risk of chronic HBV infection. One approach was a 'screen, vaccinate or initiate management' strategy and the other a 'vaccinate only' strategy. A cohort of 26,548 refugees who arrived in Minnesota and Georgia during 2005–2010 was evaluated to determine the prevalence of chronic HBV infection. The estimated six-year period-prevalence of chronic HBV infection was 6.8% in the overall refugee population. While the up-front costs of the screening strategy were higher than 'vaccinate only', the 'screen, vaccinate or initiate management' proposal displayed a positive net benefit. The major benefit drivers for the screening policy are earlier medical management of chronic HBV infection and averted lost societal contributions from premature death.

### 6.10.5 Tables and Figures

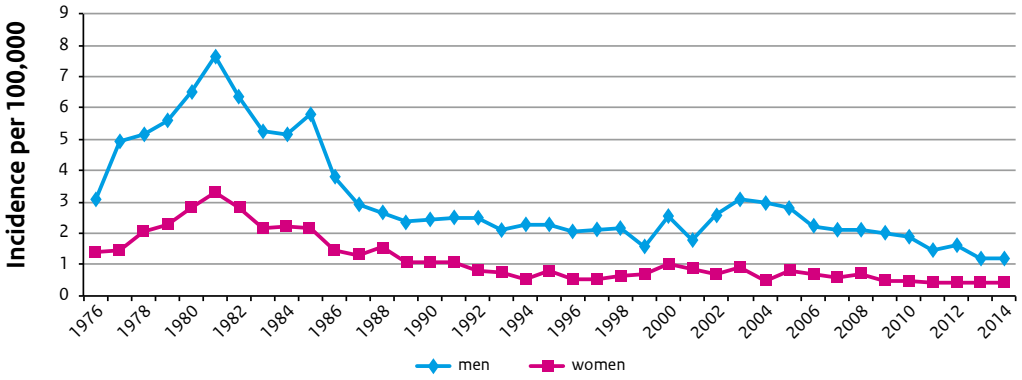


**Figure 6.10.1** Incidence of acute HBV infections (notifications) in men and women in the Netherlands between 1976 and 2014

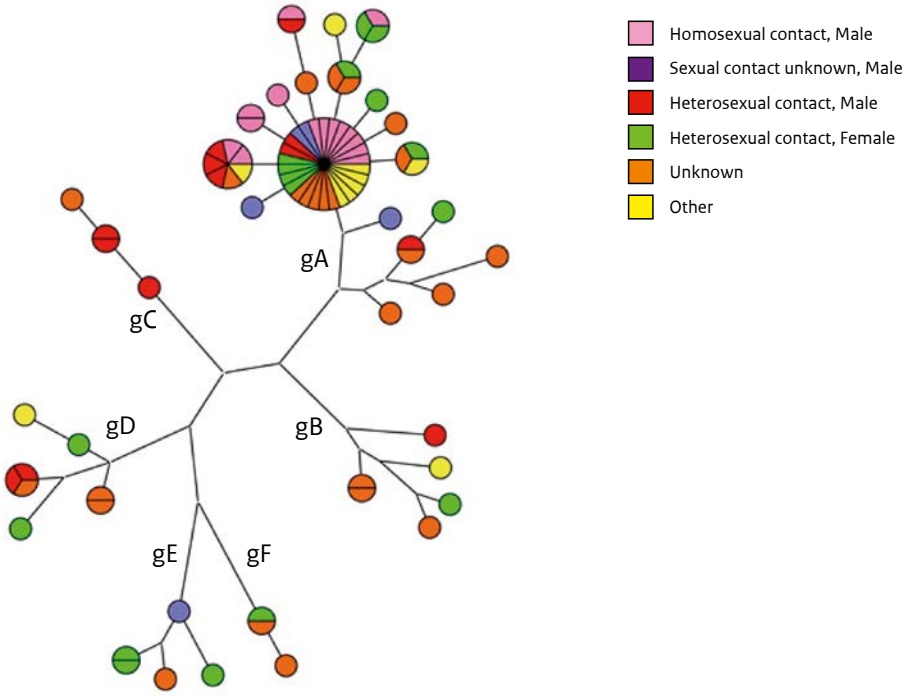


**Figure 6.10.2** Minimum spanning tree based on the S-region sequence of acute HBV cases in the Netherlands in 2014 by reported risk factor (n=88)

### 6.10.6 Literature


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* RIVM publication

## 6.11 Pneumococcal disease

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### 6.11.1 Key points

- Introduction of pneumococcal conjugate vaccination (PCV) led to a significant decrease in overall invasive pneumococcal disease (IPD), especially in the vaccine target group of children under 5 years and the elderly aged 65 and older, due to herd protection.
- Introduction of 7-valent PCV (PCV7) in 2006 decreased vaccine-type IPD from 7.4 per 100,000 per year in 2004-2006 to less than 1 per 100,000 per year in 2013-2015.
- The switch to 10-valent PCV (PCV10) in 2011 reduced the number of IPD cases caused by the additional PCV10 serotypes (1, 5 and 7F) in the vaccine-eligible age groups.
- A decrease in incidence of IPD caused by the additional PCV10 serotypes in the adult age groups was seen in 2013-2015. This is probably due to herd protection as a result of PCV10 introduction for children, although longer follow-up is needed to establish this since natural fluctuations in time cannot be ruled out yet.
- The incidence of non-vaccine-type IPD increased after the introduction of PCV7. The increase in 2013-2015 was very small. This was mainly due to a decrease in serotype 19A IPD. The decrease in 19A IPD probably reflects natural fluctuation, but may also be due to cross-protection by PCV10 or a new balance between serotypes over time.

### 6.11.2 Epidemiology

#### *6.11.2.1 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.

#### *6.11.2.2 Overall IPD*

Overall, IPD incidence decreased significantly by 11% since the introduction of PCV7 in 2006. The decrease was largest in the major affected age groups of children <5 years and the elderly aged 65 years and older (Figure 6.11.1).

#### *6.11.2.3 Vaccine type IPD*

In the last 2 years (period June 2013-May 2015), the overall incidence of IPD caused by PCV7 serotypes was less than 1 per 100,000 per year, indicating a large and sustained effect of PCV7 introduction in vaccinated and unvaccinated age groups (Figure 6.11.2). The switch to PCV10 in 2011 decreased the incidence of IPD caused by the three additional serotypes in PCV10 in vaccine-eligible age groups. For example, there were 0 cases of serotype 1, 5 and 7F in the <2 years age group in the last 2 years in the sentinel surveillance (Figure 6.11.3). In the nationwide

surveillance, the number of cases in <2-year-olds clearly decreased after 2011 with only 1 case of serotype 1, 5 or 7F in 2014 and 1 case up to May 2015 (Figure 6.11.4). Figure 6.11.2 also shows a significant decrease in incidence of IPD caused by the additional PCV10 serotypes in the adult age groups in 2013-2015. This is probably due to herd protection as a result of a reduction in the carriage and transmission of the three additional serotypes in vaccinated children, although longer follow-up is needed to firmly establish these herd effects over time.

#### *6.11.2.4 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 6.11.5 shows the increase in non-PCV10 serotype IPD). In the last two years, there was no substantial increase any longer of non-vaccine type IPD. This was partly due to a decrease in serotype 19A IPD (Figure 6.11.6). The decrease in 19A IPD was expected, since a decline in 19A carriage was also observed in 2011/12 in children (Bosch et al., submitted), who are the key transmitters of pneumococcal infections in the population. The decline in carriage and subsequent disease may be due to cross-protection by 19F in PCV10, a new balance between competitive serotypes over time or it may reflect natural fluctuation. In adults, the decline in 19A incidence probably reflects natural fluctuation, as we observed a substantially higher incidence in 2014-2015 (1.8 per 100,000) compared with 2013-2014 (1.2 per 100,000).

#### *6.11.2.5 Hospitalisation due to IPD*

The overall incidence of hospital admissions due to meningitis, sepsis and pneumonia caused by pneumococci has decreased since 2006 in the age groups targeted for pneumococcal vaccination (Figure 6.11.7). The incidence of hospital admissions in children above 5 years of age, adults and the elderly remained more or less stable.

#### *6.11.2.6 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. Together with a decline in IPD, the IPD mortality incidence decreased significantly from 2.4 per 100,000 per year in 2004-2006 to 1.7 per 100,000 per year in 2008-2012. The case fatality rate and mortality incidence were highest among patients 65 years or older (17% and 8.3/100,000 respectively in 2008-2012).
In 2014 and 2015, 70 IPD cases among children aged 5 years or younger were reported nationally. For 44 cases, the mortality status was known. Three of the 44 cases (6.8%) died. These three cases had non-vaccine type IPD (serotype 15C, 22F and 23A) and one had comorbidity.

#### *6.11.2.7 Vaccine failure*

Since the introduction of PCV7, there have been 43 cases of vaccine-type IPD among vaccine-eligible children in the nationwide surveillance. Of these, 16 children (37.2%) were vaccinated with at least 2 doses (Table 6.11.1). Six of these children had serotype 19F IPD. In 2014 and 2015, there were two 7F vaccine failure cases. Serotype 7F is one of the three additional serotypes in PCV10 as compared with PCV7.

### 6.11.3 Pathogen

Some changes in the characteristics of the pneumococcal strains isolated from IPD patients have been observed. For serotypes 1 and 12F there was a significant shift in clonal lineage within the serotype in the post vaccine era, compared with the years before the introduction of the vaccine. Isolates in the new clonal lineage within serotype 12F were significantly more associated with pneumonia than with other clinical syndromes. Therefore, not only serotype, but also clonal lineage may influence the clinical outcome.

### 6.11.4 Research

#### *6.11.4.1 IPD in risk groups*

Using clinical data on IPD cases from June 2008 – May 2012 and data on the prevalence of risk conditions from 2012, we calculated the incidence and case fatality of IPD in normal-risk, medium-risk and high-risk groups. IPD incidence in adults with immunocompromising conditions (high-risk group) and non-immunocompromising comorbidities (medium-risk group) were compared with the 'normal-risk group' without diagnosed comorbidities. Adults with a high-risk condition have a 18-fold and 3-fold higher risk for IPD at age 18-64 years and 65 years and older, respectively. In case of a medium-risk condition, the risk is 5-fold and 2-fold higher in age groups 18-64 and ≥65 years old. Likewise, IPD patients with a high-risk or medium-risk condition have a higher case-fatality (after adjustment for age, 2-fold and 1.4-fold, respectively). Several serotypes (e.g. 6A, 6B, 23A and 23B) are associated with a significantly higher propensity to cause disease in high-risk patients. The risk for IPD and death in the post-PCV7 era has remained considerably higher in adults and the elderly with underlying conditions. The identification of serotypes with a high propensity to affect risk groups is important for selecting (future) vaccine serotypes.

#### *6.11.4.2 Increase in empyema*

Clinical data of IPD cases from June 2004 – May 2012 showed that invasive pneumonia incidence increased in the 5-64 year-old age group from 4.92 to 5.58 cases/100,000/year (RR 1.13, 95%CI 0.99-1.29). Empyema incidence significantly increased in the elderly 65 years and older, from 0.62 to 2.60 cases/100,000/year (RR 4.28, 95%CI 1.97-9.33), mainly due to serotype 1. The incidence of other clinical syndromes, including meningitis and bacteraemia without or with other focus, decreased or stayed constant after PCV7 introduction. Serotype 1 is included in PCV10 and therefore the observed increase in empyema may decline again when herd effects of PCV10 occur.

#### *6.11.4.3 Hospitalisations of pneumonia*

Pneumonia remains an important cause of morbidity and mortality in all age groups. Until the mid-2000s, there was an increasing trend in hospitalisations due to pneumonia in the USA and Europe, which was also seen in the Netherlands. Although the aetiology of pneumonia is polymicrobial, *Streptococcus pneumoniae* is the leading cause of (bacterial) pneumonia, accounting for 20-60% of all cases.
To study the impact of infant PCV vaccination on hospital-treated primary pneumonia (HTPP) hospitalisations in all age-groups, inpatient discharge codes were collected from the National Medical Registration (LMR) for the years 1999-2005 (pre–PCV7) and 2008-2012 (post-PCV7).

HTPP was defined as a main discharge diagnosis for all-cause pneumonia, or meningitis, septicaemia or empyema together with pneumonia as a secondary discharge diagnosis. A notable, statistically significant decrease in the trend was seen for the age groups 0-6 months, 6 months-1 year, 50-64 years and 65 years and older, in which the observed annual decrease was respectively 17.5% (95%CI 16.2-20.0%), 8.8% (95%CI 6.8-10.9%), 4.0% (95%CI 3.9-4.0%) and 5.9% (95%CI 5.9-6.9%). A reduction in absolute number of hospitalisations due to HTPP was seen in all age groups in the last two observed epidemiological years, although these reductions were not statistically significant for the 0-6 year-olds and 50-64 year-olds in both epidemiological years and for those 65 and older in 2010/2011. For the entire post-PVC period, in comparison with the pre-PCV period, we observed a 30% reduction of the HTPP hospitalisation rate in children and a 6-16% reduction in adults, with only the result for the age group of 65 years and older reaching statistical significance. When vaccine-eligible children were compared with non-vaccine-eligible children, a significant reduction in HTPP hospitalisation was observed for 0-6 month-olds (IRR 0.68, 95%CI 0.64-0.73), 1-2 year-olds (IRR 0.85, 95%CI 0.80-0.89) and 2-3 year-olds (IRR 0.86, 95%CI 0.81-0.92), whereas no reduction was observed among 3-4 and 4-5 year-old children.

### 6.11.5 (Inter)national developments

#### *6.11.5.1 Efficacy of PCV13 in elderly*

In the Netherlands, a randomised, double-blind, placebo-controlled trial in 84,496 elderly ≥65 years of age was conducted to determine the vaccine efficacy (VE) of 13-valent PCV (PCV13) [1]. The primary endpoint was the first episodes of vaccine-type pneumococcal community-acquired pneumonia (VT-CAP) and the secondary endpoints were non-bacteremic/non-invasive VT pneumococcal CAP (NB/NI VT-CAP) and VT invasive pneumococcal disease (VT-IPD). In the per-protocol analysis, the first episodes of VT-CAP occurred in 49 and 90 subjects in the PCV13 and placebo group, respectively (VE 45.56%, 95.2%CI: 21.82-62.49); in 33 and 60 subjects for NB/NI VT-CAP (VE 45.00%, 95.2%CI: 14.21-65.31); and in 7 and 28 subjects for VT-IPD (VE 75.00%, 95%CI: 41.43-90.78). All-cause CAP occurred in 747 and 787 subjects in the PCV13 and placebo group, respectively (VE 5.08%, 95%CI: -5.05-14.24).

#### *6.11.5.2 Cost-effectiveness*

In the Netherlands, the cost-effectiveness of vaccinating older adults against pneumococcal disease with PCV13 was examined [2]. A probabilistic cohort model with a Markov-type process depicting the risk of clinical and economic outcomes of pneumococcal disease (IPD and CAP), as well as the expected impact of PCV13 vaccination in older adults, was developed. A base-case scenario of PCV13 versus no vaccine was evaluated in adults aged 65-74 years (n=1.5 million), assuming a 70.7% PCV13 uptake. The ICER for base-case PCV13 vaccination strategy was € 8,650/QALY (95%CI: 5,750-17,100). PCV13 vaccination of high-risk individuals aged 65-74 years was most cost-effective (i.e. cost saving) and extension to medium-risk individuals aged 65-74 years yielded an ICER of € 2,900.
In the UK, the cost-effectiveness of vaccinating the elderly and at-risk adults with the 23-valent pneumococcal polysaccharide vaccine or 13-valent pneumococcal conjugate vaccine was assessed [3]. A Markov model was used to track one UK-based cohort of individuals assuming PPSV23, PCV13 or no vaccination until death. The ICER was estimated at £8,413 when

PPSV23 was compared with no vaccination; PPSV23 dominated PCV13. Despite reductions in invasive pneumococcal diseases incidence in adults and a protection of vaccination of less than 10 years, PPSV23 was the most cost-effective option.
Wu et al. conducted a review of economic evaluations, published since 2006, of conjugate pneumococcal vaccines in children [4]. At current prices, both PCV13 and PCV10 were judged preferable to PCV7. The uncertainty related to price differences, burden of disease, vaccine effectiveness, and indirect effects determine the preference base for either PCV10 or PCV13. The crucial assumptions and results also depended on which manufacturer sponsored the study. Therefore, decision-makers using these analyses should not rely solely on an analysis from a single manufacturer.

#### *6.11.5.3 Correlates of protection*

Andrews et al. performed a post-licensure assessment of serotype-specific vaccine effectiveness (VE) and immunogenicity in England, Wales and Northern Ireland to derive the correlates of protection for individual serotypes [5]. For the 706 cases of invasive pneumococcal disease included in the study, PCV13 vaccine effectiveness after two doses before age 12 months or one dose from 12 months on was 75% (95%CI: 58–84). VE was 90% (95%CI: 34–98) for the PCV7 serotypes and 73% (95%CI: 55–84) for the six additional serotypes included in PCV13. Protection was shown for four of the six additional PCV13 serotypes (VE for serotype 3 was not significant and no cases of serotype 5 infection occurred during the observation period). The VE for PCV13 and PCV7 was lower than predicted by the aggregate correlate of protection of 0.35 µg/mL used during licensing. Calculated serotype-specific correlates of protection were higher than 0.35 µg/mL for serotypes 1, 3, 7F, 19A and 19F, and lower than 0.35 µg/mL for serotypes 6A, 6B, 18C and 23F. Opsonophagocytic antibody titres of 1 in 8 or higher did not predict protection. Although use of the aggregate correlate of protection of 0.35 µg/mL has enabled the licensing of effective new PCVs, serotype-specific correlates of protection vary widely.

#### *6.11.5.4 Antibiotic prescriptions*

A study in the Netherlands compared the use of respiratory antibiotics in the pre-PCV and post-PCV vaccination period [6]. They found that the proportion of respiratory antibiotic prescriptions fell by 4.9% (95%CI: 4.6-5.3) and 9.0% (95%CI: 2.8-14) after the introduction of the 7-valent vaccine in children aged three and four years, respectively. After the introduction of the 10-valent vaccine, a reduction of 13% (95%CI: 2.8-22), 20% (95%CI: 13-26), 17% (95%CI: 3.1-28), 22% (95%CI: 3.7-37) and 24% (95%CI: 2.4-40) was observed in two, three, four, six and seven year-old children, respectively. These results indicate a reduction in respiratory antibiotic prescriptions in young children after the introduction of the pneumococcal vaccines, although it was an ecological study and other factors could have contributed to the reduction.

#### *6.11.5.5 Next generation vaccines*

The disadvantage of currently available vaccines, 23-valent pneumococcal polysaccharide vaccine (PPSV23) and PCVs, is that they are serotype-specific. Vaccines that provide broader protection, such as recombinant protein (Phase I), Protein-plus-conjugate (phase II) and inactivated whole-cell (Phase I) vaccines, are being developed.

## 6.11.6 Tables and Figures

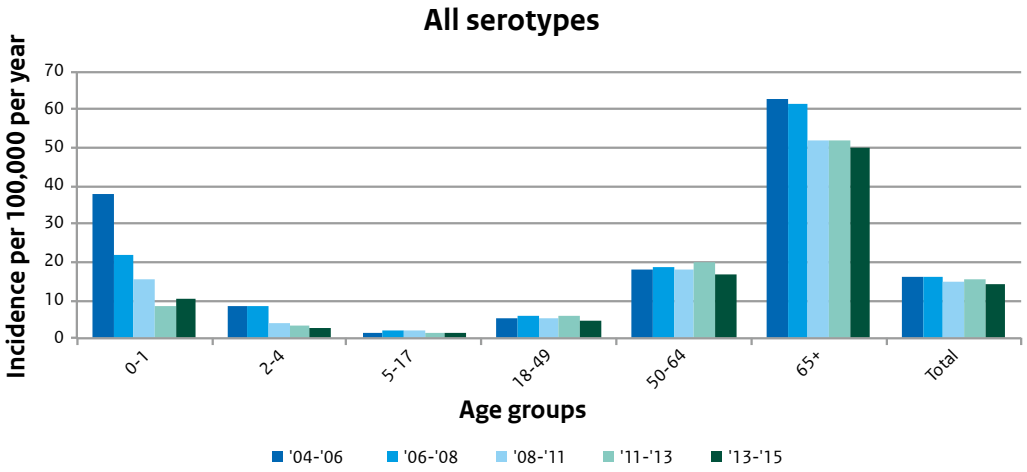


**Figure 6.11.1** Incidence of IPD caused by all serotypes, presented by age group and time period ('04-'06 = June 2004-May 2006, '06-'08 = June 2006-May 2008, etc.)

PCV7 was introduced in June 2006 and PCV10 in May 2011. Data of sentinel surveillance are used and extrapolated to the Dutch population.
Source: NRBM

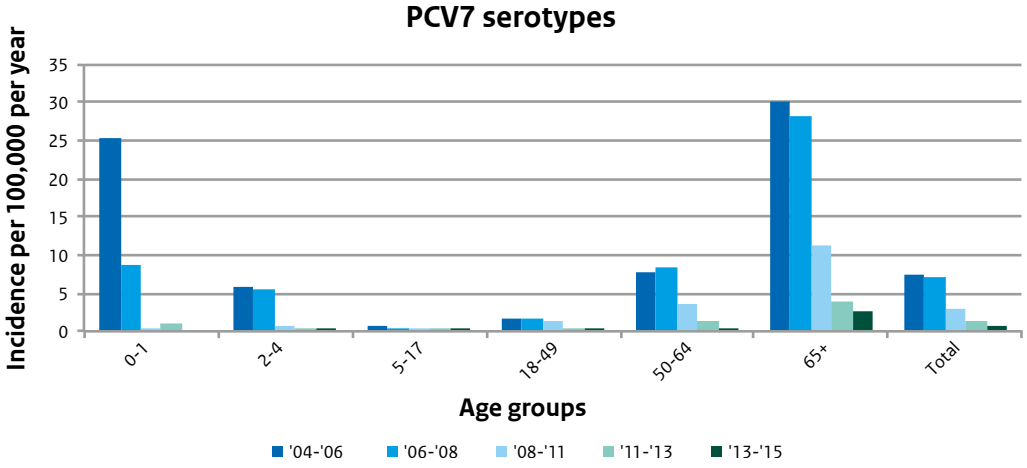


**Figure 6.11.2** Incidence of IPD caused by PCV7 serotypes, presented by age group and time period ('04-'06 = June 2004-May 2006, '06-'08 = June 2006-May 2008, etc.)

PCV7 was introduced in June 2006 and PCV10 in May 2011. Data of sentinel surveillance are used and extrapolated to the Dutch population.
Source: NRBM

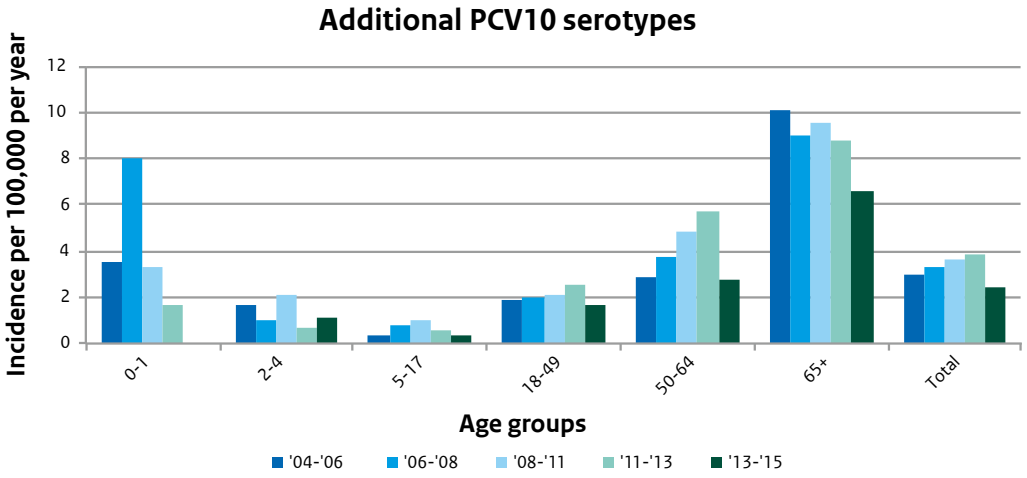


**Figure 6.11.3** Incidence of IPD caused by additional PCV10 serotypes (1, 5 and 7F), presented by age group and time period ('04-'06 = June 2004-May 2006, '06-'08 = June 2006-May 2008, etc.)

PCV7 was introduced in June 2006 and PCV10 in May 2011. Data of sentinel surveillance are used and extrapolated to the Dutch population.
Source: NRBM

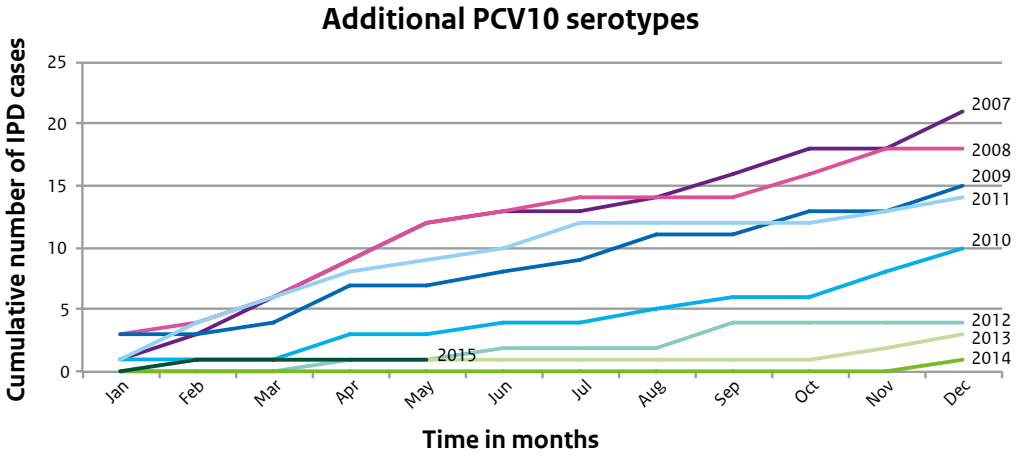


**Figure 6.11.4** Cumulative number of IPD cases caused by the additional PCV10 serotypes (1, 5 and 7F) in children < 2 years of age

PCV10 was introduced in March 2011. Data of nationwide surveillance are used.
Source: NRBM

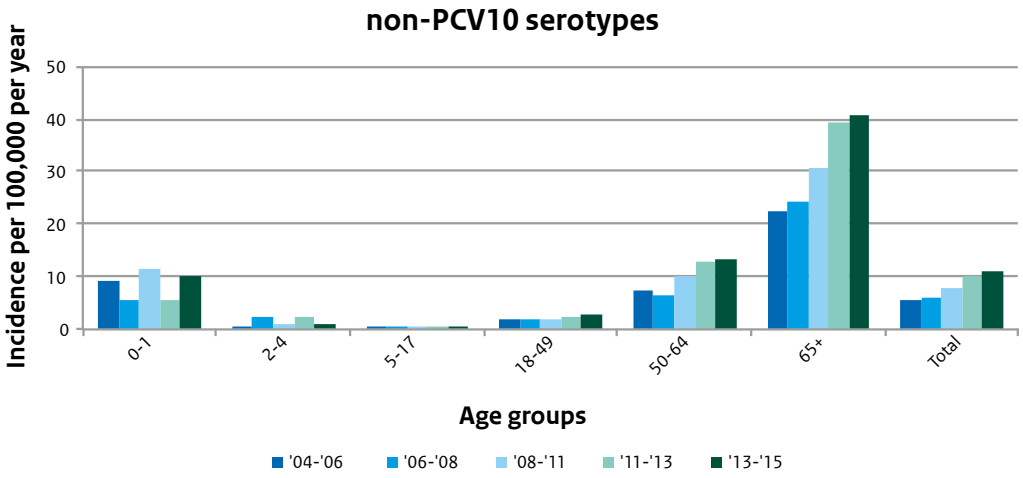


**Figure 6.11.5** Incidence of IPD caused by non-PCV10 serotypes, presented by age group and time period ('04-'06 = June 2004-May 2006, '06-'08 = June 2006-May 2008, etc.)

PCV7 was introduced in June 2006 and PCV10 in May 2011. Data of sentinel surveillance are used and extrapolated to the Dutch population.
Source: NRBM

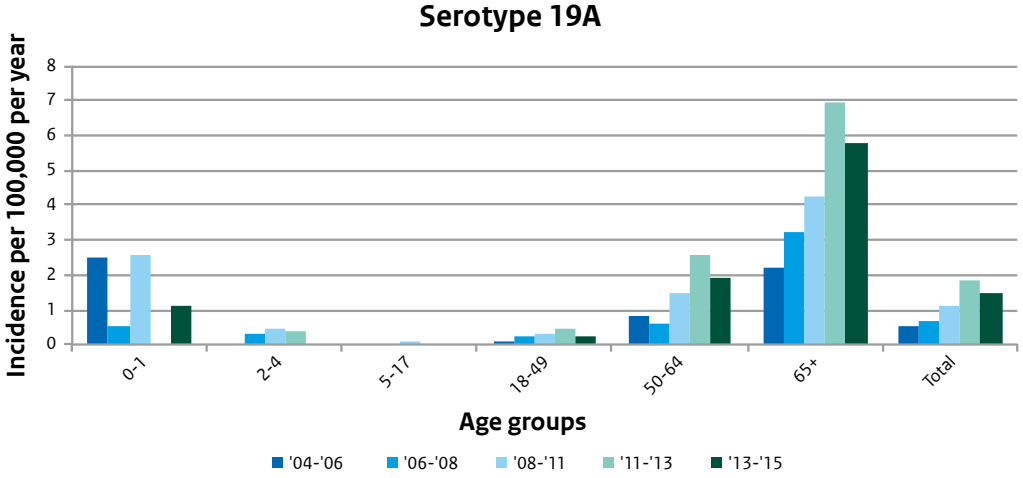


**Figure 6.11.6** Incidence of IPD caused by serotype 19A, presented by age group and time period ('04-'06 = June 2004-May 2006, '06-'08 = June 2006-May 2008, etc.)

PCV7 was introduced in June 2006 and PCV10 in May 2011. Data of sentinel surveillance are used and extrapolated to the Dutch population.
Source: NRBM

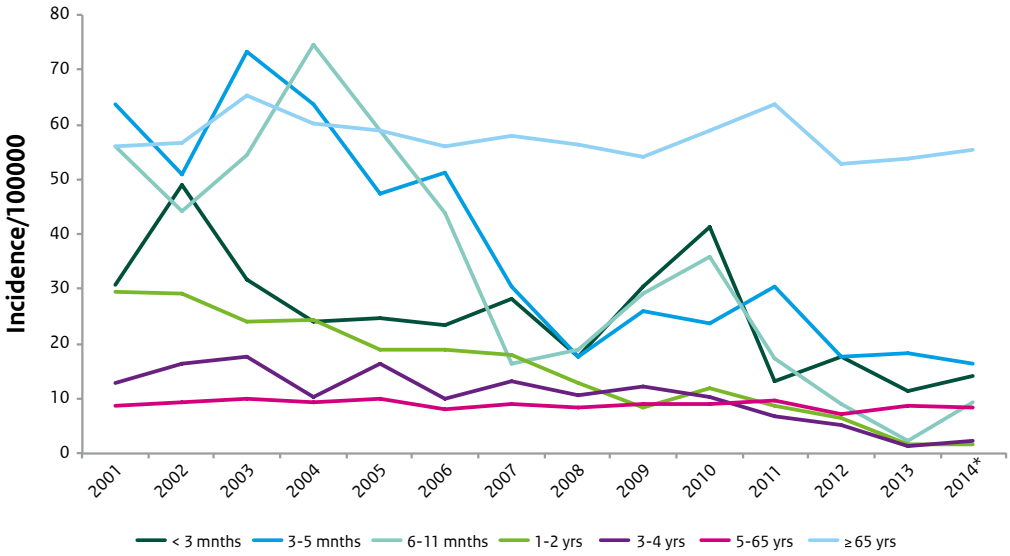


**Figure 6.11.7** Age-specific incidence of hospitalisation due to pneumococcal disease (i.e. pneumococcal meningitis, pneumococcal septicaemia, pneumococcal pneumoniae and pneumoniae by Streptococcus)

* For 2014, the hospitalisation data are preliminary and incomplete.
Source: DHD

**Table 6.11.1** Children with vaccine type IPD who received at least 2 vaccinations based on nationwide surveillance data using data up to May 2015

| 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 | Leukaemia |
| 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 |
| 2014 | 18 | 7F | PCV10 | 4 | - |
| 2014 | 41 | 23F | PCV10 | 4 | Beta thalassemia with chronic blood transfusions |
| 2015 | 13 | 7F | PCV10 | 4 | - |

### 6.11.7 Literature


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## 6.12 Human papillomavirus (HPV) infection

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### 6.12.1 Key points

- Incidences of human papillomavirus (HPV)-associated cancers and death related to HPV-associated cancers have slightly increased in the last decade in the Netherlands.
- Vaccine effectiveness of the bivalent vaccine against incident and persistent infections in a cohort study was high up to four years post-vaccination.
- Persistent HPV16/18 infections were found to have significantly higher baseline viral loads than clearing infections.
- Antibody avidity after a two-dose schedule (0, 6 months) was not remarkably different from a three-dose schedule, indicating comparable quality of the antibody response.

### 6.12.2 Epidemiology

A persistent HPV infection with a high risk HPV (hrHPV) type is a necessary cause in the development of cervical cancer. It can also cause vaginal, vulvar, penile, anal, mouth/oral and oropharyngeal cancer. hrHPV 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 the tongue [1]. Figure 6.12.1 and Figure 6.12.2 present the incidences of HPV-associated cancers and deaths related to HPV-associated cancers, for absolute numbers of cervical cancers see Appendix 2. The non-oncogenic low-risk HPV (lrHPV) types 6 and 11 can cause genital warts (GW). In 2014, the number of GW diagnoses at sexually transmitted infections (STI) clinics was 2,029 [2]. The percentage of diagnoses of GW by the number of consults decreased from 2.9% in 2009 to 1.4% in 2014. The number of diagnoses of GW by GPs has slightly increased since 2009 and was estimated at 36,552 in 2013.

From 2014 onwards, all Dutch girls up to 14 years of age will receive the bivalent (HPV16/18) HPV-vaccine in a two-dose vaccination schedule (0, 6 months).

### 6.12.3 Pathogen

Besides genotyping, pathogen surveillance activities focus on intratype variation in the L1 protein of HPV16/18 viruses. Intratypic molecular variants of HPV16 and HPV18 exist. Long-term vaccination with the L1 protein could lead to shifts in the genetic diversity of the HPV16/18 virus population. In order to detect shifts in the genetic diversity, we have determined the genetic diversity at the start of vaccination through the molecular sequencing of the entire L1 gene of HPV16 and HPV18 virus strains isolated in 2009 and 2011. As HPV variants have been shown to differ in geographic origins, it was to be expected that European HPV16 and HPV18 variants were identified most frequently in the Dutch isolates. Indeed, the majority of our isolates concerned variant lineages, 93% and 86% for HPV16 and HPV18, respectively, similar to the European reference strain and the strains used in the vaccine.

### 6.12.4 Research

#### *6.12.4.1 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 vaccinated and unvaccinated young women. Vaginal self-swabs collected in this cohort were tested for the presence of HPV DNA. Four years after vaccination, 1,244 swabs were tested, 27.3% were positive for any HPV and 19.9% were positive for a hrHPV type. Among vaccinated participants, HPV51, 56 and 58 were the most prevalent hrHPV types. Among unvaccinated participants HPV51, 52 and 16 were the most prevalent hrHPV types. VE against incident and persistent infections was determined. The bivalent vaccine is effective against HPV16/18/31/45 incident and persistent infections at least 4 years post-vaccination (Table 6.12.1).

In addition, the long-term effectiveness and immunogenicity for alternate dosage schedules among participants of the HAVANA study was examined. Due to limited sample size, no hard conclusions could be drawn. GMCs for two doses at 0 and 6 months were comparable to three doses, although, due to the limited sample size, the non-inferiority comparison was inconclusive. Risk difference in infection rates was non-inferior for two doses, compared with three.

#### *6.12.4.2 Genital warts among vaccinated and unvaccinated women (PASSYON)*

Data from the UK [3] and from a vaccine trial [4] suggested that the bivalent vaccine, which is currently used in the Netherlands, might offer protection against GW. We investigated the effect of the bivalent vaccine on GW and genital HPV6/11 positivity, using data from a repeated cross-sectional study among 16 to 24 year-old STI-clinic visitors (PASSYON study) [5]. Of the 385 female study participants who were eligible for vaccination in the NIP, 55.1% were reported to be vaccinated. Among the vaccinated women, 0.5% were diagnosed with GW and 11.8% tested positive for vaginal HPV6/11. Among the unvaccinated women, these figures were 2.3% and 13.3%, respectively. Although not statistically significant, the vaccinated women had lower odds of acquiring GW than the unvaccinated women (OR 0.2; 95%CI 0.02-1.8). No effect on HPV6/11 positivity was observed (OR 0.9; 95%CI 0.5-1.6). Adjustment for demographics and sexual behaviour did not change these effects. There are indications that the bivalent vaccine offers protection against GW, although we cannot draw definite conclusions due to the low incidence of GW.

#### *6.12.4.3 Differences in development of sexual behaviour among HPV vaccinated and unvaccinated girls*

This longitudinal observational study asks both vaccinated and unvaccinated girls about their knowledge of HPV and about their sexual behaviour and examines whether this changes differently over time. General knowledge of HPV and of HPV transmission increased for both the vaccinated and unvaccinated participants. The vaccinated girls were more likely to have stated that (offering) HPV vaccination had changed their sexual behaviour. The vaccinated girls were more likely to be sexually active at the start of the study. The proportion of those sexually active increased to a greater degree over time among the vaccinated girls than it did among the unvaccinated girls, although there were no large differences in the number of casual or steady partners.

#### *6.12.4.4 HPV16/18 Viral Load*

The HPV viral load is a marker for the productivity of an infection at a specific time point. High viral load has been associated with persistent infections. HPV vaccination is expected to have effects on vaccine types HPV16 and HPV18 in the Netherlands. The vaccine has been shown to prevent persistent infection, but not necessarily transient infections. It can therefore be expected that vaccination will reduce the average HPV16/18 viral load in vaccinated girls. Monitoring changes in viral load values could lead to further insights into infection development.

To detect a possible change in viral load, highly sensitive quantification assays targeting HPV16/18 L1 have been implemented. The sensitivity of these real-time (RT) PCRs has been found to approach that of the $SPF_{10}$-DEIA-$LIPA_{25}$ platform used for HPV detection.
The assay has been applied in the Chlamydia trachomatis Screening and Implementation (CSI) study. Persistent HPV16/18 infections were found to have significantly higher viral loads than clearing infections (p=0.015 for HPV16 and p=0.018 for HPV18). Furthermore, an infection of HPV16 simultaneously with another HPV type was found to have a significantly higher viral load than HPV16 alone (p=0.003), for HPV18 the viral load was not influenced by co-infections (p=0.138). Predicting persistent infections based on single viral load measurements proved elusive, even when integrating both viral load and HPV co-infection status into a model. However, every log-unit increase of viral load led to higher odds of infections persisting (OR=1.29, 95%CI=1.11-1.51 and OR=1.26, 95%CI=1.06-1.51 per log-unit for HPV16 and HPV18, respectively). In addition, a trend was observed for participants with HPV co-infections other than HPV16. These participants were more likely to have a persistent infection (OR=1.58, 95%CI=0.87-2.89, p=0.135). For HPV18, this trend was not observed (OR=1.62, 95%CI=0.54-4.85, p=0.392).

#### *6.12.4.5 HPV16/18 Whole Genome Sequencing*

HPV is a highly conserved double stranded (ds) DNA virus, in which minimal variation occurs as a result of evolution. Comparing sequences from longitudinal study samples could therefore provide enough resolution to discriminate between true persisting infections and same-type reinfection events. Samples were obtained from the CSI study, which has up to four sample rounds per participant. HPV16 and HPV18 whole genome Sanger sequencing assays were developed at the RIVM. Full sequence coverage is required to be able to compare sequences obtained from different rounds. Preliminary results indicated that most infections were truly persistent. The HPV16 genome variants were identical through round one and two for all but one participant. The diverging participant was infected with a European HPV16 variant in round one and an Asian-American variant in round two. Sequencing of data from round three and four is in process.

#### *6.12.4.6 Monitoring the implementation of the two-dose schedule (HPV-2D)*

For monitoring the change from a three-dose to a two-dose vaccination schedule, a study which consists of two parts was set up. Firstly, a retrospective cross-sectional serological evaluation was performed among girls who had received three doses or two doses (at least 5 months apart) of the bivalent HPV vaccine (birth cohorts 1997-2000). For vaccine types HPV16 and HPV18, seroprevalence was 100% up to 4 ½ years after the first dose, irrespective of the schedule. GMCs for vaccine types after a two-dose schedule were not non-inferior (NI margin for GMC ratio 2.0) to a three-dose schedule at all-time points, except for HPV18 at two to three years after the first dose. For the antibody avidity of vaccine types, non-inferiority could not be concluded, mainly based on inconclusive non-inferiority comparisons, except for HPV16 at three to four years after the first dose, for which non-inferiority could be concluded. Although the non-inferiority of antibody avidity could not be concluded, no remarkable differences were found. Secondly, this study consists of a still ongoing cohort study being conducted among the first birth cohort that was eligible for vaccination with a two-dose schedule, i.e. birth cohort 2001. For at least one and a half years, these girls will be monitored for the quality and quantity of the generated immune response.

#### *6.12.4.7 Systematic review of a comparison between two-dose and three-dose immunogenicity*

In a systematic review and meta-analysis, the comparability of antibody levels between and within different age groups was evaluated. For both the bivalent and quadrivalent vaccine, a two-dose immunisation of girls yielded non-inferior GMCs relative to a three-dose schedule in young women up to, respectively, 48 and 36 months of follow-up. Pooled GMC ratios for the bivalent vaccine within girls showed the two-dose schedule becoming inferior to the three-dose schedule in girls for HPV16 at approximately two years after the first dose. For the quadrivalent vaccine, antibody responses for HPV18 became inferior from 18 months of follow-up onwards when comparing the two-dose schedule with the three-dose schedule within girls. The implementation of two-dose HPV vaccination needs to be monitored closely.

#### *6.12.4.8 Tolerability of the two-dose schedule*

After the implementation of the two-dose schedule in the Netherlands, tolerability following this new schedule was monitored by the RIVM. Local and systemic AEs occurring within the 7 days following each dose were obtained by online questionnaires. We also obtained online questionnaires on symptoms occurring in the week before vaccination. A local reaction was reported by 86.1% and 81.9%, respectively, after the first and second doses. A general symptom was reported by 73.0% and 71.6% following the first and second doses, respectively. The most reported local reactions were pain (1st dose: 71.7% and 2nd dose: 74.9%) and reduced use of the arm (1st dose: 63.0% and 2nd dose: 52.3%). With respect to the general symptoms, myalgia (1st dose: 60.7% and 2nd dose: 56.8%), fatigue (1st dose: 19.3% and 2nd dose: 25.9%) and headache (1st dose: 21.1% and 2nd dose: 17.7%) were the most reported. But general symptoms in the week before vaccination occurred just as often, or sometimes even more often, as they did after vaccination. The tolerability of the first dose of the two-dose schedule was more favourable compared with the first dose of the former three-dose schedule. For the dose at six months, the tolerability was comparable for both schedules.

#### *6.12.4.9 HPV and HIV (H2M)*

In cross-sectional studies, HPV prevalence is consistently higher among HIV-infected people. Few studies have been done to establish the incidence and clearance rates of hrHPV infections in relation to HIV. The HIV and HPV in MSM (H2M) study is a prospective cohort study in which approximately 750 HIV-negative and HIV-infected MSM aged 18 years or older were tested every half year for anal and penile HPV DNA. The study was conducted in Amsterdam between 2010 and 2013, and the follow-up for each participant lasted 24 months.

The incidence of hrHPV was high in this sexually active population: the incidence rate of anal HPV-16 infection was 9.1 per 1,000 person-months in HIV-infected men and 4.7 per 1,000 person-months in HIV-uninfected men. The incidence of hrHPV was consistently higher among the HIV infected men (<0.001). Although the clearance rate of those men with an anal infection was high, a substantial proportion of those with hrHPV at baseline were still infected 24 months later (e.g. for HPV18: 46% and 37%, respectively). The results indicate that the prevalence of anal hrHPV among HIV-infected men is high, because both the incidence is higher and the clearance rate is lower [6, 7].

#### *6.12.4.10 Serology*

The serological assay measuring antibodies against seven hrHPV types is based on the recognition of the antibodies to epitopes on distinct virus-like particles (VLPs). It is key to ensure the supply of the VLPs for future research, which is mainly in hands of the vaccine production companies. In addition to the seven hrHPV types, it is desirable to include HPV6 and HPV11 as well, which would enable us to monitor the seroprevalence against these GW-related HPV types.

#### *6.12.4.11 Modelling*

We extended the means to model the sero-epidemiology of HPV16 by a mixture model in two ways: first, by incorporating serological measurements on another HPV type in a so-called bivariate mixture model; and second, by informing the rate of transition from seronegative to seropositive by the force of infection from a transmission model. The first extension showed that the classification of individuals with antibody concentrations around the laboratory cut-off for seropositivity can be improved in a bivariate relative to the univariate mixture model. It also suggested that the seroprevalence of HPV16 might be somewhat underestimated in a univariate model. This supposition was also borne out by linking the serological mixture model to a transmission model for HPV16. In doing so, we estimated around 75% of women seroconvert after an incident HPV infection, and that seropositivity is naturally lost at a rate of around 2% per year. These estimates imply that univariate seroprevalence estimates offer a lower boundary for the proportion of women who have been in contact with HPV16 [8].

We also assessed the reduction in the vaccine-preventable burden of cancer in men if boys are vaccinated along with girls against oncogenic HPV types 16 and 18 by means of Bayesian evidence synthesis. We evaluated the impact of vaccination against HPV types 16 and 18 on the burden of anal, penile and oropharyngeal carcinomas among heterosexual men and MSM.

We estimated that before HPV vaccination, around 15 QALYs per thousand men were lost to vaccine-preventable cancers associated with HPV in the Netherlands. Assuming that vaccination also prevents secondary transmission, this burden would be reduced by 37% if the vaccine uptake among girls remains at the current level of 60%. To prevent one additional case of cancer among men, 795 boys would need to be vaccinated; with tumour-specific numbers for anal, penile and oropharyngeal cancer of 2,162, 3,486 and 1,975, respectively. The burden of HPV-related cancer in men would be reduced by 66% if vaccine uptake among girls increased to 90%. In such an event, 1,735 boys would need to be vaccinated to prevent an additional case; with tumour-specific numbers for anal, penile and oropharyngeal cancer of 2,593, 29,107, and 6,484, respectively. The incremental benefit of vaccinating boys when vaccine uptake among girls is high is driven by the prevention of anal carcinomas, which underscores the relevance of HPV prevention efforts for men who have sex with men [9].

### 6.12.5 International developments

#### *6.12.5.1 Effectiveness*

A systematic review and meta-analysis to assess population-level consequences and herd effects after female HPV vaccination (both bivalent and quadrivalent vaccine) programmes showed a significant decrease in HPV16 and HPV18 infections between pre-vaccination and post-vaccination periods of 68% (RR 0.32 95%CI 0.19-0.52). Additionally, a reduction was also seen for HPV31, HPV33 and HPV45, which indicates cross-protection. Among countries using the quadrivalent vaccine, a decrease in GW in girls eligible for vaccination was seen, but also in older women and boys younger than 20 years of age, which indicates herd effects. In countries with vaccine coverage below 50%, indications for cross-protection or herd effects were absent, although this could be due to the indirect nature of the inferences in this study [10]. The final event-driven analysis of the PATRICIA trial, with a mean follow-up of 39 months, shows that in the HPV naïve group vaccine efficacy against cervical intraepithelial neoplasia (CIN) 1+, CIN2+ and CIN3+ associated with HPV16 or HPV18 were, respectively, 96.5% (95%CI 89.0-89.4%), 98.4% (95%CI 90.4-100%) and 100% (95%CI 64.7-100%). So vaccinating adolescents before sexual debut has a substantial impact on the incidence of high-grade cervical abnormalities [11].

#### *6.12.5.2 Cost-effectiveness*

Two studies, in Canada and the UK, were conducted to evaluate the cost-effectiveness of a two-dose HPV vaccination schedule [12, 13]. The studies concerned men and women and also took non-cervical cancers into account. Both studies concluded that a two-dose schedule is likely to be the most cost-effective option if protection lasts for at least 20 years. As the precise duration of protection provided by two-dose schedules may not be known for decades, cohorts given two doses should be closely monitored.

Olsen et al. assessed the cost-effectiveness of extending the universal HPV vaccination to both girls and boys in Denmark, including the prophylactic effects on all potentially vaccine preventable HPV-associated diseases in males and females [14]. The ICER of vaccinating girls only was estimated to be € 3,583 per QALY gained in a 3-dose regime. The ICER of vaccinating girls and boys compared with girls only was € 28,031 and € 41,636 per QALY gained, in a two-dose and three-dose regime, respectively. Given a cost-effectiveness threshold of € 50,000 per QALY gained in Denmark, the vaccination of boys and girls was valued to be cost-effective.

#### 6.12.5.3 *Males*

In 2011, the USA was the first country that recommended the HPV vaccine for males for routine administration. Since that date, several countries have followed, such as Austria, Australia and several provinces of Canada. In the USA, the uptake of HPV vaccination in 2014 among males was 41.7% [15].

#### 6.12.5.4 *Nonavalent vaccine*

In March 2015, the EMA adopted a positive opinion for the marketing authorisation of a nonavalent HPV vaccine (Gardasil 9, Merck and Co., Inc) [16]. This nonavalent vaccine is indicated, in a three-dose schedule (0, 2, 6 months), for the active immunisation of females and males from the age of 9 years against the following HPV diseases: i) premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types 16, 18, 31, 33, 45, 52 and 58; ii) genital warts caused by HPV types 6 and 11.

Joura et al. investigated the efficacy and immunogenicity of the nonavalent HPV vaccine in women aged 16 to 26 years [17]. In this study an efficacy of 96.7 (95%CI 80.9-99.8) against high-grade cervical, vulvar, and vaginal disease related to HPV types 31, 33, 45, 52 or 58 was estimated in the per-protocol population. Antibody levels for HPV6/11/16/18 were, at one month after the third dose, non-inferior compared with the levels after the quadrivalent vaccine. A higher number of injection-site-related AEs were reported after the nonavalent vaccine (90.7% of participants) than were reported after the quadrivalent vaccine (84.9% of participants), and events with severe intensity were also more common after the nonavalent vaccine [17, 18]. Serious AEs related to the vaccine were rare [19].

Since February 2015, the Advisory Committee on Immunization Practices (ACIP) has recommended the nonavalent HPV vaccine as one of the three vaccines that can be used for routine HPV vaccination in the US [20]. In the US, the nonavalent vaccine was estimated to potentially prevent from 4.2% to 18.3% of the invasive cervical, anal, oropharyngeal and vaginal cancers in addition to the current vaccines for both males and females [21]. Serrano et al. estimated a potential additional impact of the nonavalent HPV vaccine compared with the current vaccines of 12 to 19% on HPV-related invasive cervical cancer in Brazil, Mexico, India and China [22]. In France, the additional impact of the nonavalent vaccine compared with the quadrivalent vaccine was potentially 9.9 to 15.3% for invasive cervical cancer, 24.7 to 33.3% for high-grade cervical neoplasias, 12.3 to 22.7% for low-grade squamous intraepithelial lesions and 8.5 to 10.4% for anal cancer [23]. A low efficacy benefit of 2.1 to 5.4% was found for genital warts and of 0.0 to 1.6% for oropharyngeal carcinoma, which could be explained by the fact that these conditions are almost exclusively associated with HPV types targeted by the quadrivalent vaccine.

Kiatpongsan et al. determined the vaccine costs for which the nonavalent HPV vaccine would be cost-effective compared with the current bivalent and quadrivalent vaccines in Kenya and Uganda [24]. They estimated that the nonavalent vaccine would be very cost-effective if the added cost per vaccinated girl is between 5.2 (worst-case scenario) and 16.2 (best-case scenario) International dollars in Kenya and between 4.5 (worst-case scenario) and 13.7 (best-case scenario) International dollars in Uganda.

Kosalaraksa et al. evaluated the immunogenicity and safety of the nonavalent vaccine when administered concomitantly with REPEVAX (a diphtheria, tetanus, pertussis and poliomyelitis

vaccine) in females and males 11-15 years of age [25]. Concomitant administration of the vaccines was generally well-tolerated. For all types of the nonavalent HPV vaccine, non-inferiority of GMC (non-inferiority margin GMC ratio 0.5) and seroconversion rates (non-inferiority margin difference -5%) for the concomitant versus the non-concomitant group was demonstrated.

#### *6.12.5.5 Safety*

Both the EMA and Lareb have announced a review of the current notifications of complex regional pain syndrome and postural orthostatic tachycardia syndrome in relation to HPV vaccination; former reports on these conditions among women who had received the HPV vaccine, in which a causal link was not established, were considered by the EMA.

### 6.12.6 Tables and Figures

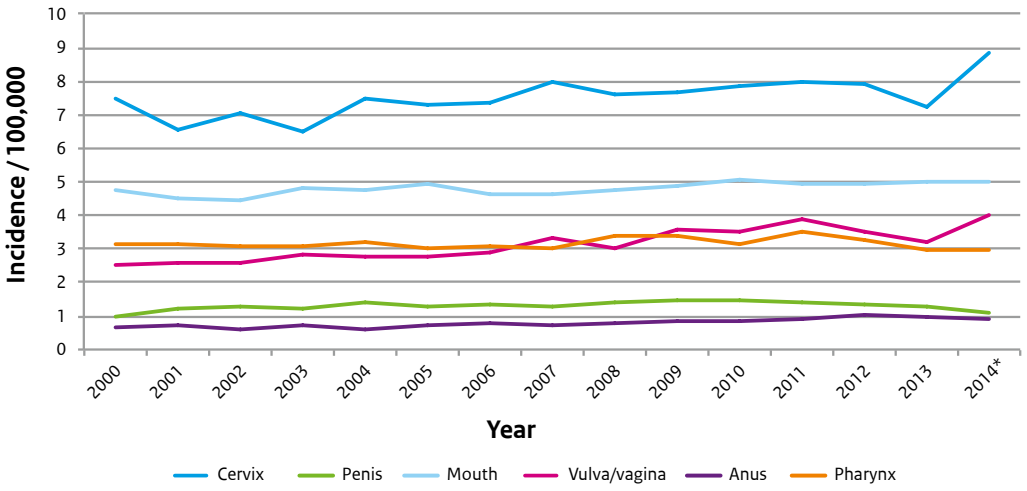


**Figure 6.12.1** Incidence / 100,000 (standardised by the European standardised rate) of new cervical, anogenital, mouth/oral and pharynx/pharyngeal cancer cases in the Netherlands 2000-2014, by cancer type (the Netherlands Cancer Registry (NKR))

*Preliminary figures

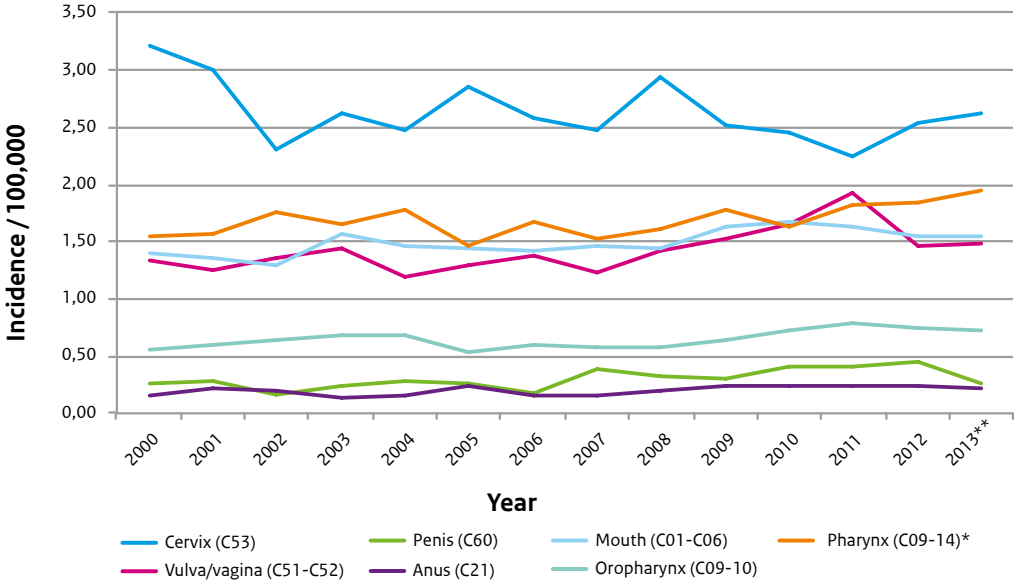


**Figure 6.12.2** Incidence / 100,000 of deaths related to cervical, anogenital, mouth, oropharynx and pharynx cancer cases in the Netherlands 2000-2013 by cancer type (Statistics Netherlands (CBS))

* Number of deaths due to pharynx cancer includes the number of oropharynx cancer deaths.
** Preliminary figures. In 2013, CBS started to use international software for automatically coding the causes of death. This makes the number more reproducible and internationally comparable. Due to this change, there have been some significant shifts seen in the causes of death.

**Table 6.12.1** Vaccine effectiveness (VE) up to four years post-vaccination

| | Crude VE | 95% CI | Adjusted VE* | 95% CI |
|---|---|---|---|---|
| **Incident infections** | | | | |
| HPV16 and 18 | 69% | (50%-81%) | 70% | (52%-82%) |
| HPV16,18,31,45 | 73% | (60%-82%) | 72% | (58%-82%) |
| | | | | |
| **Persistent infections** | | | | |
| HPV16,18 (#) | 100% | ## | 100% | ## |
| HPV16,18,31,45 (#) | 76% | (-16%-95%) | 86% | (58%-95%) |
| HPV16,18 | 65% | (25%-84%) | 75% | (44%-89%) |
| HPV16,18,31, 45 | 62% | (27%-80%) | 69% | (39%-84%) |

HPV = human papillomavirus;
* Adjusted for the following baseline characteristics: age, urbanization degree, education, ethnicity, ever smoked, currently smoking, contraception use, ever had sexual intercourse, age of partner, lifetime number of sexual partners
# Negative for one of these types at baseline
## Model does not converge

### 6.12.7 Literature


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* RIVM publication

# 7
# Future NIP candidates

## 7.1 Rotavirus infection

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### 7.1.1 Key points

- In 2014, the rotavirus season was exceptional low.
- G9P[8] was the most prevalent genotype in 2014.
- The relative prevalence of G2P[4] shows a slight, but steady increase since 2011.

### 7.1.2 Epidemiology

The Working Group Clinical Virology reports the number of rotavirus positive results weekly. In 2014, the rotavirus season was exceptionally low and delayed in the winter/spring in the Netherlands (Figure 7.1.1). In total, 607 diagnoses were reported in 2014, compared with 1,487 diagnoses in 2013 and 1,287 in 2012 (Table 7.1.1). After the low season of 2014, an extra high season was expected in the winter of 2014-2015. However, up to July 2015, the season was comparable to 2012, which had been a low season (see Figure 7.1.1). All-cause gastroenteritis in children under the age of 5 was examined using routine health record data from general practices in the Nivel Primary Care Database for comparison with the weekly rotavirus reports [1]. These data correlated well with the weekly number of rotavirus positive results, with a significant decrease occurring between August 2013 and August 2014. The cause of this drop in rotavirus in the Netherlands in 2014 is unknown. Some potential contributing mechanisms mentioned in the literature are the mild winter of 2013/2014, the relatively high rotavirus epidemic season of the winter of 2012/2013, declining birth rates over the years, thus decreasing the group of susceptible individuals, and rotavirus vaccination programmes in neighbouring countries [1-4].
Recent studies suggest that there is a slight increase in the risk of intussusception among babies after receiving the first dose of rotavirus vaccine [5-9]. After the second and third doses, this risk is marginally elevated. As a result of these findings, baseline incidences of intussusception are calculated for the Netherlands to observe a possible increase after the introduction of rotavirus vaccination (see Chapter 5, Table 5.3 and Table 5.4).

### 7.1.3 Pathogen

IDS/RIVM received 137 faeces samples that tested positive for rotavirus in peripheral laboratories, 130 of these samples could be typed (Table 7.1.1). G1P[8] was no longer the most prevalent genotype in 2014. The most prevalent genotype in 2014 was G9P[8]. Worthy of note is the slight, but steady increase of relative prevalence of G2P[4] since 2011 (Figure 7.1.2). Mixed rotavirus infections are known to occur in approximately 5% of the cases, but will not readily be detected by this sequence-based method.

### 7.1.4 Research

IDS/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 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 2009-2014 are given in Section 7.1.3 and Figure 7.1.2.
This multicentre study, Risk-Group Infant Vaccination Against Rotavirus (RIVAR), started in December 2014. This Phase IV study assesses the effectiveness, impact and feasibility of a rotavirus vaccination programme organised through secondary paediatric care and targets high-risk infants, including children born prematurely, with low birth weight or severe congenital pathology. The study pilots implementation of the RIVAR programme in several hospitals in a step-wedged design, combined with an observational before-after cohort study of high-risk infants. Enrolment of implementation across several hospitals covers a period of 3 years.
The mechanisms contributing to the rotavirus epidemic pattern and explaining the unanticipated drop in detected rotavirus cases in the 2014 season are further explored in a project initiated by the Epidemiology and Surveillance Department of the RIVM on temporal associations between rotavirus detections, birth rate and weather conditions.

### 7.1.5 International developments

As of April 1st 2015, 77 countries worldwide have implemented universal rotavirus vaccination, including 12 European countries (Armenia, Austria, Belgium, Estonia, Finland, Georgia, Germany, Latvia, Luxembourg, Moldavia, Norway and the United Kingdom) [10]. Several other countries are at various stages of issuing national recommendations or integrating rotavirus vaccination into their national immunisation programmes. In the Netherlands, a recommendation by the Health Council about including rotavirus vaccination in the NIP is expected at the end of this year. In France, however, because of three infant deaths and many serious side effects, rotavirus vaccines are no longer recommended for routine childhood immunisation (see Chapter 5) [11].

Both the orally administered live monovalent Rotarix vaccine and the orally administered live pentavalent Rotateq vaccine are marketed internationally. The monovalent live attenuated vaccine Rotavac is currently only licensed for the Indian market. Local development of other rotavirus vaccines is ongoing in the USA, Finland, India, Brazil, Australia and Vietnam [12]. These include other live (neonatal) rotavirus vaccines, as well as inactivated (subunit) rotavirus vaccines suitable for intramuscular or intradermal administration.

Post-implementation studies on the real-world impact of rotavirus vaccination now include data covering up to 7 years post-implementation. A systematic review summarised the impact of universal rotavirus vaccination in European countries and reported an effectiveness of between 68 and 98% and reductions in rotavirus-related hospitalisations of between 65 and 84% [13]. Another meta-analysis assessed strain-specific effectiveness in high and middle-income countries globally and the impact on rotavirus strain distribution using data covering up to 6 years post-implementation [14]. In high-income settings, the effectiveness of Rotarix and Rotateq was comparable, ranging from 83% to 94% for fully homotypic strains and from 71% to 87% for partly or fully heterotypic strains. Prevalent strains in countries using Rotarix were G2P[4] (2,198 of 4,428, 50%) and G1P[8] (953, 22%), and prevalent strains in countries

using Rotateq were G1P[8] (1,280 of 3,875, 33%) and G2P[4] (1,169, 30%). Sustained predominance of a single strain was not recorded. The US reported sustained reductions in rotavirus detections up to 7 years post-implementation in the CDC passive laboratory reporting system, the National Respiratory and Enteric Virus Surveillance System (NREVSS) [15]. The decline compared with pre-vaccination ranged between 58% and 90% in each of the 7 post-vaccine years. The biennial pattern of rotavirus activity that emerged in the post-vaccine era in the US was sustained, with years of low activity and highly erratic seasonality alternating with years of moderately increased activity and seasonality similar to that seen in the pre-vaccine era. Annual rotavirus-coded hospitalisation rates in the US also declined by 63-94% in the post-vaccine years 2008-2012 [16].

The European Society for Paediatric Infectious Diseases updated their consensus recommendations for rotavirus vaccination in Europe [17]. The recommendation to vaccinate all infants against rotavirus and that the first dose of oral rotavirus vaccine should be given between 6 and 12 weeks of age has been sustained, but with an emphasis toward the lower range of the recommended age, that is, preferably between 6 and 8 weeks of age in order to minimise the risk of rotavirus vaccination induced intussusception. An update of literature on intussusception and other AEs of rotavirus vaccination is given in 5.3.2.5.

### 7.1.6 Tables and Figures

**Table 7.1.1** Number of reported laboratory diagnoses of rotavirus, and number of positive samples sent to and typed at the RIVM, 2009-2014

| | | Samples at RIVM | | Samples typed at RIVM | |
|---|---|---|---|---|---|
| Year | Laboratory diagnoses | 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 |
| 2014 | 607 | 137 | 22.6 | 130 | 94.9 |

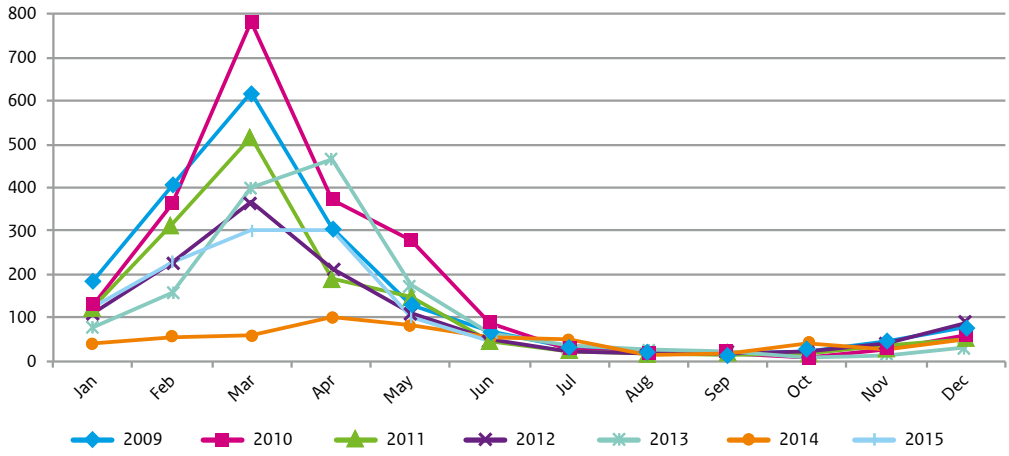


**Figure 7.1.1** Reported laboratory diagnoses of rotavirus per month, 2009-2014

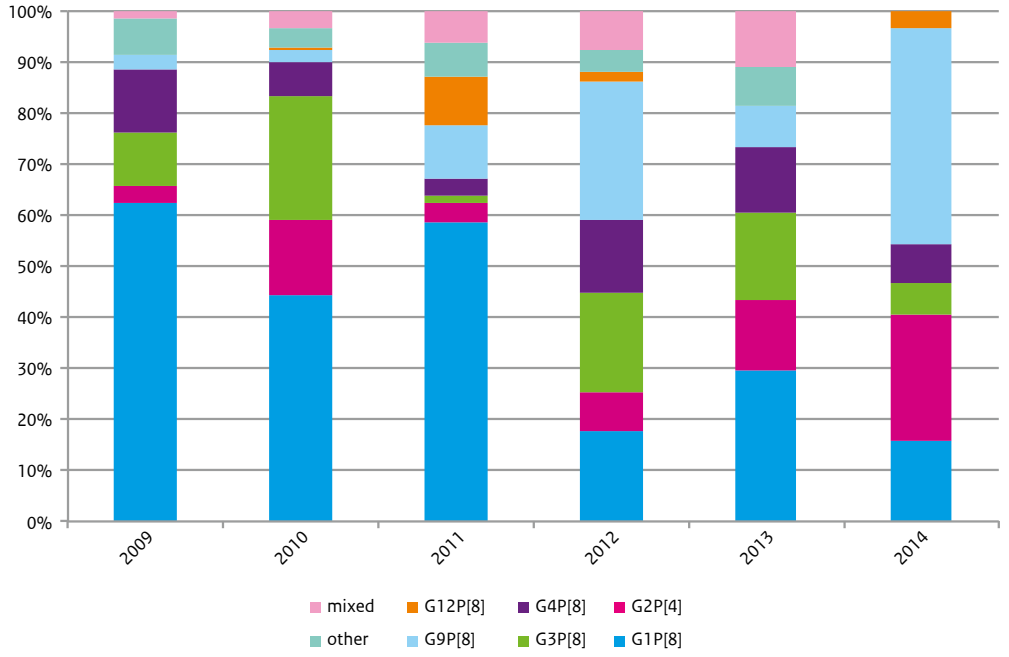


**Figure 7.1.2** Rotavirus types as genotyped at the RIVM, 2009-2014

### 7.1.7 Literature


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* RIVM publication

## 7.2 Varicella zoster virus (VZV) infection

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### 7.2.1 Key points

- The VZV epidemiology (incidence of GP consultations, hospitalisations and deaths) is comparable to previous years.
- It has been hypothesised by Hope-Simpson that exogenous immune boosting in latently infected persons by contact with varicella patients reduces the probability of herpes zoster. If true, universal varicella vaccination may increase herpes zoster incidence due to reduced varicella zoster virus circulation.
- The cost-effectiveness of varicella vaccination is strongly affected by its impact on herpes zoster and the time horizon for economic assessment: in the absence of exogenous immune boosting, varicella vaccination with high coverage is expected to be cost-effective and may even be cost saving, while it is not expected to be cost-effective on reasonable time scales if immune boosting is present. Results by birth cohort show that varicella vaccination may result in inequalities of the health effects between generations.

### 7.2.2 Epidemiology

According to a new, more precise method for estimating morbidity rates used by NIVEL from 2012 onwards, the incidence of herpes zoster is higher than it was according to the old method (Table 7.2.1) [1, 2]. The new method uses constructed episodes of illness (episodes are closed after 4 and 16 weeks without an encounter for varicella and herpes zoster, respectively), based on an algorithm instead of the recorded 'raw' episodes of care in the old method. Because of these changes, the incidence for 2010-2012 was recalculated. In the period 2010-2013, 2.2% of the patients with a new varicella episode had more than one new episode in the same year, for herpes zoster this was 2.5%. The incidence of varicella episodes per 100,000 of 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 7.2.1). 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 7.2.2 and Table 7.2.2).
Mahamud et al. found that 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 their 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 2014, we would expect 4.2 deaths (range 1.7–6.4) instead of the 26 deaths that were reported in 2014 (Table 7.2.3).

### 7.2.3 Pathogen

In 2015, an overview has been published concerning the current progress towards understanding the molecular mechanisms that account for the reduced virulence of vaccine virus [4]. A complicating factor in research into genetic factors that contribute to a lower pathogenicity of the OKA vaccine strain is the fact that the strain contains a mixture of genetically distinct haplotypes (i.e. not all genomes contain the vaccine changes at all positions). The three commercial vaccine strains differ in their sequence and genetic heterogeneity is observed between vaccine lots from the same manufacturer. Depledge et al. describe how the haplotype of Varivax is different in every skin lesion [5]. Rash-forming haplotypes are not completely representative of the virus population. They found no significant differences in allele frequencies between viruses directly causing rash after vaccination and those that cause a zoster-rash following a period of latency and reactivation.

### 7.2.4 Research

In 2015, a cost-effectiveness analysis of varicella vaccination in the Netherlands, including its effects on herpes zoster, has been finalised [6]. The effects of varicella vaccination were simulated using a dynamic transmission model, parameterised with varicella zoster prevalence [7] and herpes zoster incidence data [8], and linked to an economic model. In this study, a two-dose varicella vaccination programme with a first dose at 12 months and a second dose at 4 years of age was simulated starting on January 1, 2020 under various vaccination coverages. It has been hypothesised by Hope-Simpson [9] that exogenous immune boosting in latently infected persons by contact with varicella patients reduces the probability of herpes zoster. If true, universal varicella vaccination may increase herpes zoster incidence due to reduced varicella zoster virus circulation in the population. Furthermore, the varicella vaccine contains a live attenuated virus, which itself can cause reactivation. However, there is limited quantitative evidence on the frequency of herpes zoster among varicella vaccinees, especially over the long term [10]. We therefore considered four vaccination scenarios (labelled A-D) that differ by whether or not they include exogenous immune boosting and whether or not reactivation of vaccine virus is included (see Table 7.2.4).

The impact of vaccination on the incidence of varicella and herpes zoster by birth cohort is shown in Figure 7.2.3. The four scenarios yield identical results for varicella and differ substantially for herpes zoster. Specifically, in scenario B (no boosting, no reactivation of vaccine virus), both varicella and herpes zoster incidence decrease with increasing vaccination coverage in vaccinated cohorts; the incidence of varicella and herpes zoster in unvaccinated cohorts is marginally affected. In contrast, in scenario A (immune boosting, no reactivation of vaccine virus), the incidence of herpes zoster increases in comparison with scenario B not only in the vaccinated cohorts but also in unvaccinated cohorts. This is due to the reduced immune boosting in latently infected persons, which has a profound impact, especially when vaccination coverage is high. In scenario C (immune boosting, reactivation of vaccine virus) the situation is even more extreme because, in this scenario, even all vaccinated cohorts have a high lifetime risk of herpes zoster if vaccination coverage is high. In the scenarios that include boosting (scenarios A and C), the effect of vaccination on varicella and herpes zoster is much smaller in case of low to intermediate vaccination coverage (25% or 50%).

The full impact of vaccination on reducing the incidence of varicella is observed within 5 to 10 years into the vaccination programme (Figure 7.2.4). In contrast, the potential increase in herpes zoster incidence (scenarios A and C with immune boosting) occurs on a much longer timescale of 20-60 years after the start of vaccination.

Figure 7.2.5 shows a stylised overview of the cost-effectiveness analyses at high vaccination coverage (95%). In models without immune boosting (scenarios B and D), vaccination at high coverage is expected to be cost-effective (scenario D) or even cost saving (scenario B). In contrast, in models with boosting (scenarios A and C), vaccination at high coverage is either not cost-effective within 180 years (scenario C) or is cost-effective only in the very long term (>130 years; scenario A), with exception of the first ten years after the start of vaccination when varicella incidence is low and herpes zoster incidence has not yet increased. In these scenarios, disadvantages for unvaccinated birth cohorts (i.e. health loss due to increased herpes zoster) out-weigh health benefits for vaccinated cohorts.

These analyses show that the health effects and cost-effectiveness of varicella vaccination depend crucially on its impact on herpes zoster and the time horizon for economic analysis. In the absence of exogenous immune boosting, vaccination with high coverage is expected to be cost-effective and may even be cost saving, while it is not expected to be cost-effective on reasonable timescales if immune boosting is present. Results by birth cohort further reveal that varicella vaccination may result in inequalities of the health effects between generations. Specifically, in scenarios with immune boosting, the benefits of vaccination accrue in vaccinated birth cohorts, while the burden and costs are largely due to herpes zoster in unvaccinated persons. Cohorts born just before the introduction of vaccination, especially, are expected to pay the price for the health gain in vaccinated cohorts. These results reveal an ethical dilemma for policymakers, as groups not included in the vaccination programme may be exposed to a substantially increased health hazard. In conclusion, optimal decision-making on varicella vaccination will involve judicious and repeated weighing of the various scenarios as more evidence comes in from countries with vaccination programmes already in place. The results of these analyses can be used by the Dutch Health Council, which is preparing a recommendation on herpes zoster vaccination (and, in the longer run, on varicella vaccination) in the Netherlands.

### 7.2.5 International developments

Besides the guidance of ECDC on varicella vaccination [11], which was finalised in 2015, the WHO published a position paper on varicella and herpes zoster vaccines [12]. The WHO acknowledges that the public health value of varicella vaccination in lowering the varicella disease burden is well-established. It advises countries before deciding on the introduction of varicella vaccination to set up adequate disease surveillance and especially to pay attention to vaccination coverage and its possible impact on herpes zoster. Countries deciding on herpes zoster vaccination should take into account the age-dependent burden of disease, vaccine effectiveness, the duration of protection and cost-effectiveness to determine the optimal age and dosing schedule.

Continuous surveillance of varicella and herpes zoster is important since it remains difficult to draw definite conclusions on a possible effect of varicella vaccination on herpes zoster incidence [13]. Russell et al. found declining rates of herpes zoster in Alberta, Canada among persons ≤10 years, consistent with an impact of varicella vaccination. They state that the trend of increasing herpes zoster among older persons began prior to start of universal varicella vaccination in 2002 [14]. Humes et al. also detected declining rates of herpes zoster hospitalization in Connecticut, USA among persons ≤14 years [15]. They state that there are at least two possible explanations – a vaccine-induced reduction in the number of persons with latent wild varicella infection and a reduction in the prevalence of underlying conditions that are associated with a higher risk of HZ, such as HIV infection. Baxter et al. found a major reduction in varicella incidence and hospitalisation with no evidence of a shift to older age groups in the 15 years after the introduction of vaccination against varicella [16]. Kelly et al. showed decreased varicella and increased herpes zoster incidence in a setting of increasing varicella vaccine coverage in Victoria, Australia through an ecological study [17]. Severe varicella (as measured by hospitalisation) also decreased after the implementation of varicella vaccination in Spain, while the hospitalisation rate of herpes zoster slightly increased [18]. From 1 September 2013, routine vaccination against herpes zoster at 70 years of age was introduced in the UK [19].

Recently, two European economic evaluations and three reviews have been published regarding universal varicella vaccination and herpes zoster vaccination for the elderly. Péraud et al. assessed the cost-effectiveness of a herpes zoster vaccination programme in Germany using a Markov Model [20]. From a societal perspective, vaccinating 20% of people ≥60 years would result in an ICER of € 37,417 per QALY gained, whereas vaccinating 20% of people ≥50 years would lead to more favourable results: € 32,848 per QALY gained. Kawai et al. reviewed the cost-effectiveness of vaccination against herpes zoster and postherpetic neuralgia and concluded that most of the 15 included studies showed that vaccination against herpes zoster is likely to be cost-effective [21]. De Boer et al. also reviewed the cost-effectiveness of vaccination against herpes zoster [22]. They concluded that the vast majority of the fourteen included studies showed that the vaccination of 60 to 75 year-olds was cost-effective when the duration of vaccine efficacy was longer than 10 years. Another study aimed to assess the cost-effectiveness of adding routine varicella vaccination through MMRV, using different vaccination strategies in France, based on a dynamic transmission model [23]. Routine MMRV vaccination is expected to be a cost-effective option, considering a cost-effectiveness threshold of € 20,000 per QALY gained; routine vaccination was cost saving from a societal perspective. Results were driven by a large decrease in varicella incidence, despite a temporary initial increase in the number of zoster cases due to the assumption of exogenous boosting. Damm et al. reviewed 38 modelling studies that assessed the cost-effectiveness of routine varicella and herpes zoster vaccination [24]. They also concluded that vaccination against herpes zoster is mostly considered to be cost-effective, while the cost-effectiveness of varicella vaccination depends on the inclusion or exclusion of exogenous boosting in the model. Therefore, a clarification concerning the role of exogenous boosting is crucial for decision-making regarding varicella vaccination, as was also pointed out in our national cost-effectiveness analysis described in Paragraph 7.2.4.

A recent study of Morrison et al. showed that the long-term persistence of zoster vaccine (Zostavax®) efficacy is limited and depends on the outcome measure: vaccine efficacy for herpes-zoster-related burden of illness (a severity-by-duration measure of herpes zoster pain and discomfort) persisted into year 10 post-vaccination, whereas vaccine efficacy for herpes zoster incidence persisted only through year 8 [25].
A phase III study with a follow-up period of, so far, 3.2 years among older adults (≥50 years) in 18 countries, showed that the efficacy of a new adjuvanted recombinant subunit vaccine against herpes zoster (two doses two months apart) is high at 97.2% (95%CI: 96.6-97.9%) and does not depend on the age of administration (as was seen for Zostavax®) [26]. Although this new vaccine would, in principle, also be suitable for people with immunosuppression, efficacy and safety within this group were not studied.
A phase II study showed that three different formulations of the vaccine were immunogenic and well-tolerated in adults ≥60 years [27]. At this moment it is unknown when this new vaccine against herpes zoster might become available on the Dutch market or whether the vaccine efficacy will be long-lasting.

### 7.2.6 Tables and Figures

**Table 7.2.1** Estimated incidence per 100,000 of population of episodes of varicella (ICPC-code A72) and herpes zoster (ICPC-code S70), based on NIVEL-PCD, using the old method (2005-2011) and the new method (2010-2013) (rounded off to tens)

| Syndrome | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
|---|---|---|---|---|---|---|---|---|---|
| Varicella* | 190 | 300 | 210 | (160) | (110) | (180) | - | - | |
| Varicella** | 130 | 260 | 230 | 290 | 180 | 210 | 230 | - | |
| Varicella*** | | | | | | 310 | 270 | 250 | 280 |
| Herpes zoster** | 350 | 370 | 310 | 340 | 360 | 360 | 360 | - | |
| Herpes zoster*** | | | | | | 480 | 490 | 510 | 510 |

* Dutch Sentinel General Practice Network (CMR) [28]; starting in 2008, this network has changed from registration on paper to electronic reporting, which may have resulted in under-reporting of the weekly number of varicella patients. We therefore used data from NIVEL-PCD from 2008 onwards.
** NIVEL-PCD, old method [8].
*** NIVEL-PCD, new method from 2012 onwards [1]; 2010-2012 recalculated.

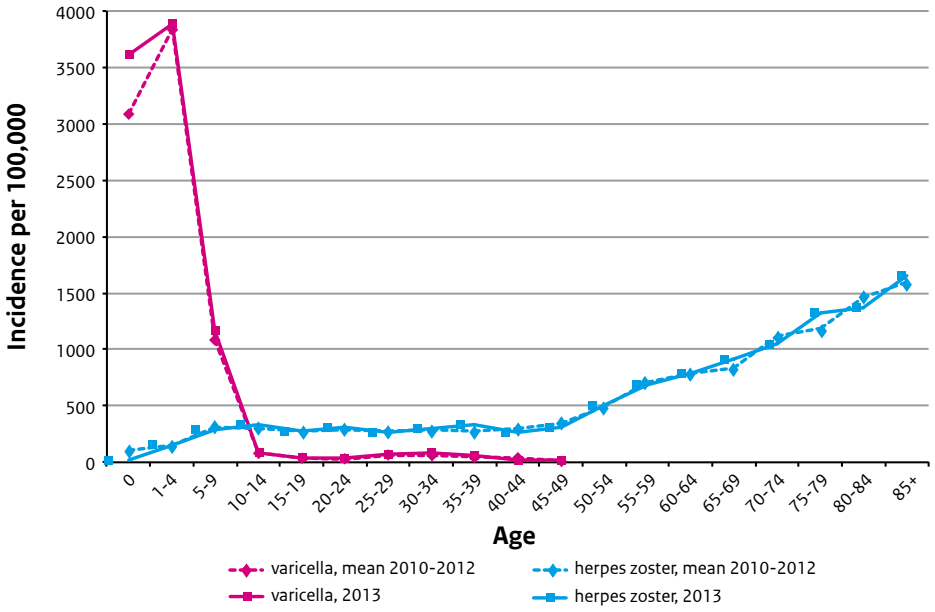


**Figure 7.2.1** Estimated incidence per 100,000 of population of episodes of varicella (ICPC-code A72) and herpes zoster (ICPC-code S70) in 2013 versus mean 2010-2012 by age group [1]

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

**Table 7.2.2** Incidence per 100,000 of population of hospitalisations due to main diagnosis of varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02), 2005–2014 [29]

| Syndrome | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014* |
|---|---|---|---|---|---|---|---|---|---|---|
| Varicella | 1.5 | 1.9 | 1.4 | 1.7 | 1.5 | 1.9 | 1.7 | 1.5 | 1.7 | 1.9 |
| Herpes zoster | 2.2 | 1.9 | 2.0 | 2.0 | 2.4 | 2.1 | 2.2 | 2.1 | 2.1 | 2.7 |

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: The number of admissions can be higher than the number of hospitalised patients reported here because some patients are admitted more than once within the same year.
* For 2014, the hospitalisation data are preliminary and incomplete.
Source: DHD

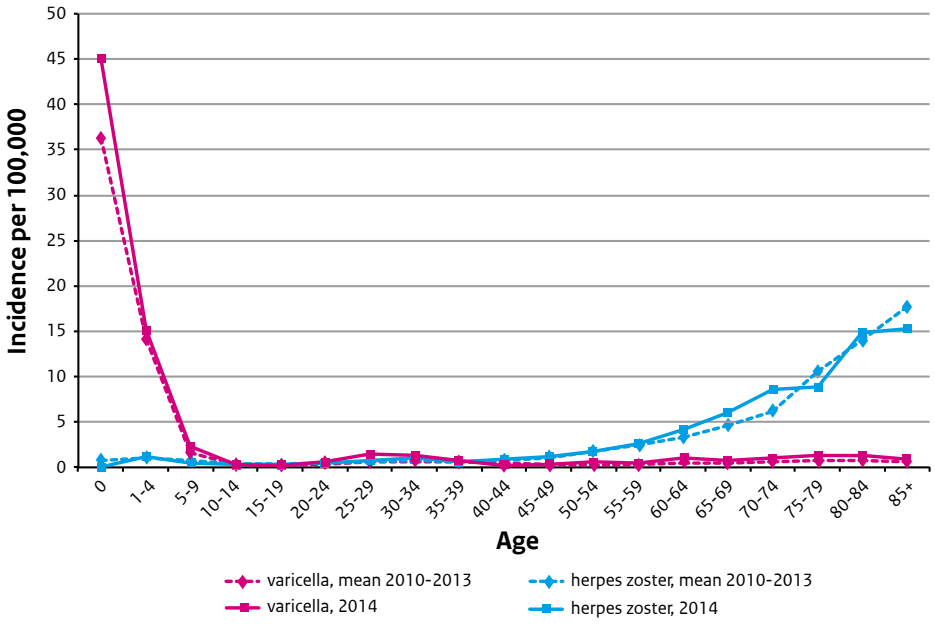


**Figure 7.2.2** Incidence per 100,000 of population of hospitalisations due to main diagnosis of varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02) in 2014 versus mean incidence in 2000-2013 by age group [29].

Note: For 2014, the hospitalisation data are preliminary and incomplete.

Source: DHD

**Table 7.2.3** Absolute number of deaths with main cause varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02), 2005–2014 [30]; data for 2013-2014 are preliminary

Source: CBS

| Syndrome | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|---|---|---|---|---|
| Varicella | 1 | 3 | 5 | 0 | 1 | 2 | 1 | 2 | 1 | 2 |
| Herpes zoster | 15 | 24 | 21 | 14 | 20 | 25 | 20 | 21 | 21 | 26 |

**Table 7.2.4** Overview of the four main vaccination scenarios implemented in the dynamic transmission model based on different assumptions about the effects of immune boosting on herpes zoster and vaccine VZV reactivation, and with various vaccination coverages

| | Vaccination scenarios[a] | | | |
|---|---|---|---|---|
| Assumptions | A | B | C | D |
| - Boosting[b] | Yes | No | Yes | No |
| - Vaccine VZV reactivation[c] | No | No | Yes | Yes |
| - Vaccination coverage (%)[d] | 0/25/50/95 | 0/25/50/95 | 0/25/50/95 | 0/25/50/95 |

[a] General assumptions for all scenarios:
- two-dose varicella vaccination programme (first dose: 12 months, second dose: 4 years of age), starting on January 1, 2020;
- vaccine effectiveness of 90% after one dose, 95% after two doses;
- probability of breakthrough in varicella after one dose: 10% per infectious contact (relative infectiousness after one dose 50%), no breakthrough in varicella after two doses.

[b] Yes = exogenous immune boosting has an effect on the probability of VZV reactivation,
No = no effects of immune boosting.

[c] Yes = vaccine VZV is able to reactivate at the same rate as wild type VZV,
No = no reactivation of vaccine VZV.

[d] 0%: baseline without varicella vaccination, 25%: conservative coverage because of expected limited acceptance of varicella vaccination due to the perceived low severity of varicella, 50%: intermediate coverage, 95%: highest coverage based on regular Dutch vaccination coverage data.

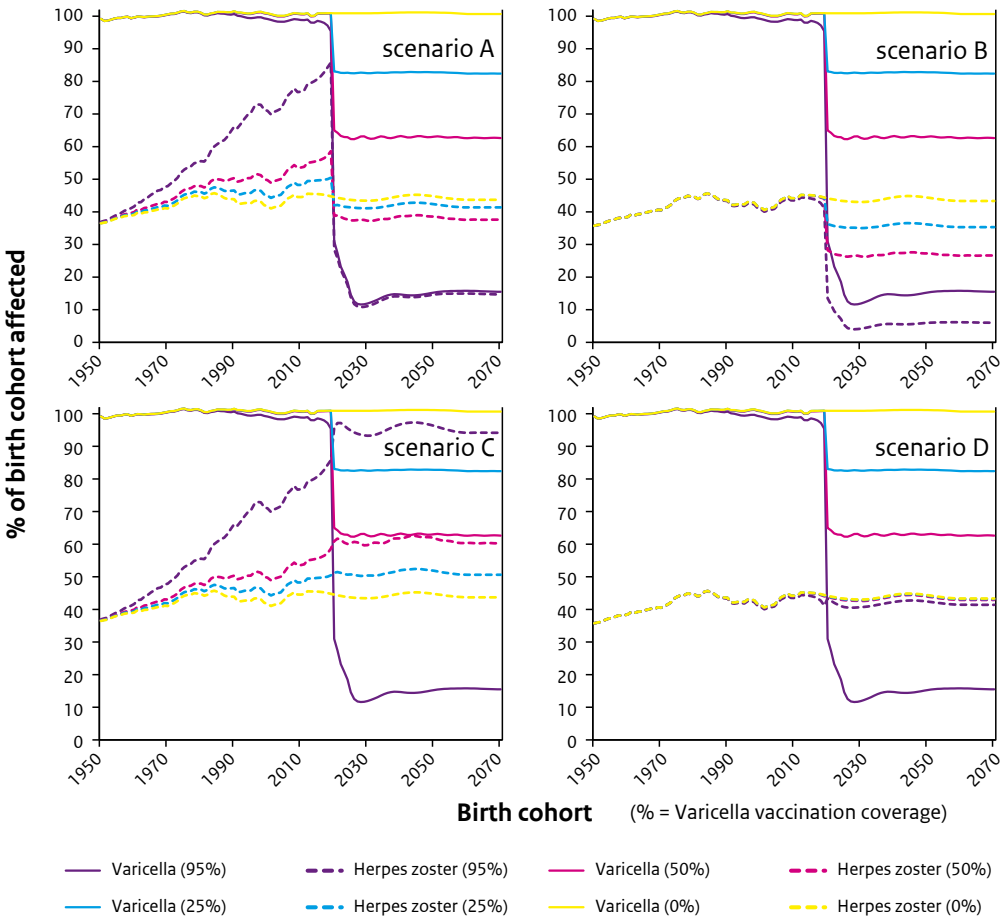


**Figure 7.2.3** Impact of varicella vaccination by birth cohort on the occurrence of varicella and herpes zoster

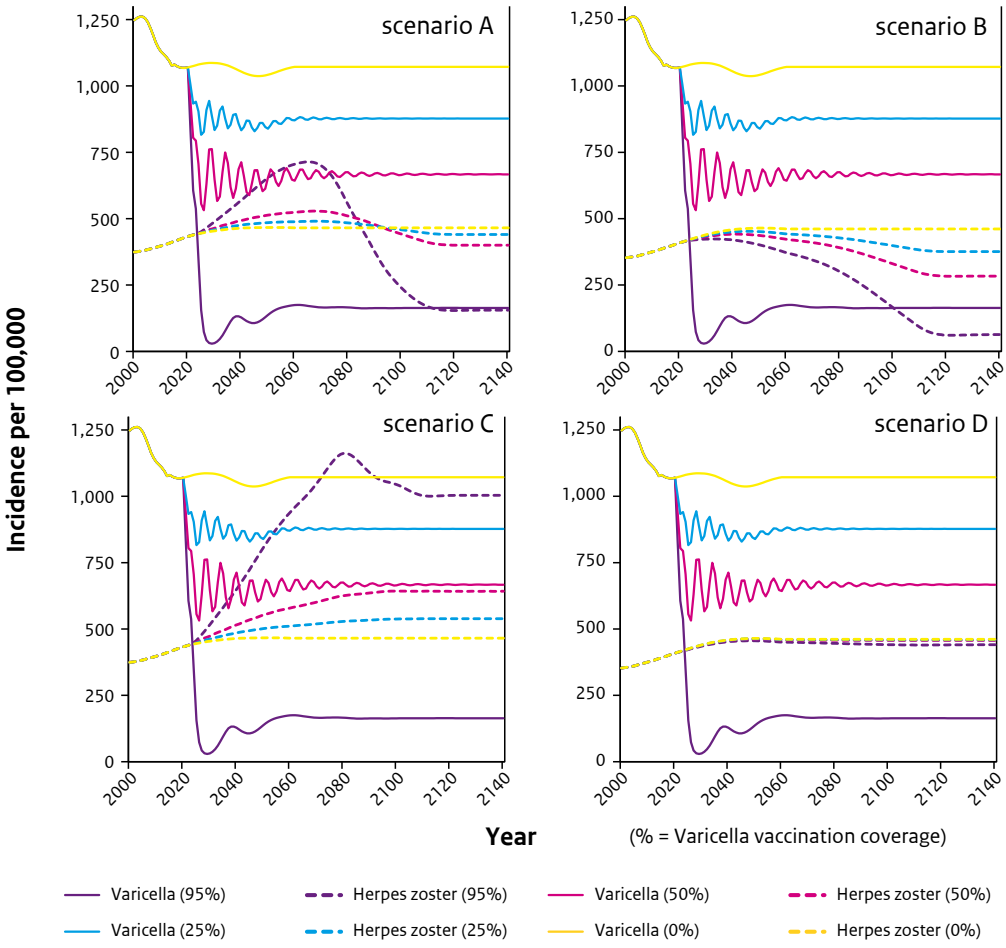


**Figure 7.2.4** Impact of varicella vaccination over time on the occurrence of varicella and herpes zoster

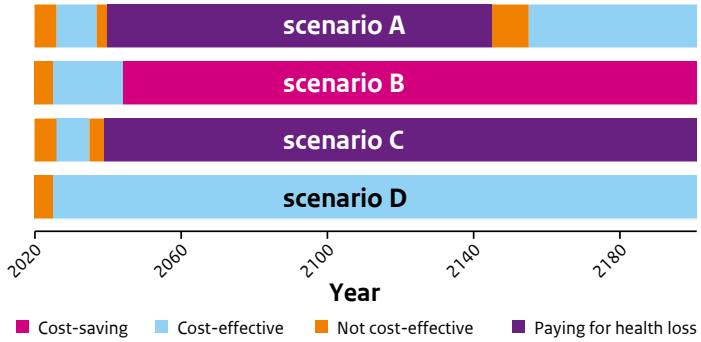


**Figure 7.2.5** Stylised overview of the cost-effectiveness of high-coverage (95%) varicella vaccination programme over time; incremental cost-effectiveness ratio (ICER) threshold is set at € 20,000 per QALY

### 7.2.7 Literature


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## 7.3 Hepatitis A

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### 7.3.1 Key points

- In 2014, the number of reported hepatitis A patients (105 cases) remained low, as in recent years.
- More than half of these patients were younger than 20 years and clusters occurred almost only amongst these cases.
- Fifty-three per cent of the Dutch cases were reported to be travel-related, almost half of them in Morocco.

### 7.3.2 Epidemiology

In 2014, 105 cases of hepatitis A were reported in the Netherlands, corresponding to 0.6 cases per 100,000 inhabitants. This is comparable to 2013 (110 cases) and the lowest number since hepatitis A became notifiable in 1999 (Figure 7.3.1 / Appendix 2). No mortality due to hepatitis A was reported. The age distribution over the years 2005-2014 is given in Figure 7.3.2. This is the first time since 2006 that more than half of the patients were younger than 20. Of the 23 patients hospitalised (22%), only 3 (13%) were younger than 20 years (5, 16 and 18 years), compared with 27% of patients hospitalised in 2013, with 13% younger than 20. Sixteen epidemiologically linked clusters with a total of 38 of the 105 cases could be deduced from the reports, only 4 clusters of which included an adult.

The percentage of travel-related cases was 53% in 2014 (Figure 7.3.1). Morocco (23/56; 41%) was reported most frequently; all other countries were reported a maximum of four times. Half of the clusters (8/16) were at least partly travel-related, mostly from Morocco (4 clusters). The consumption of food or water was reported as the source of the infection in 32% of the cases, 30/34 (88%) of which were consumed in an endemic country.

### 7.3.3 Pathogen

In 2014, from 89 (85%) cases samples were sent in for virus typing and from 73 (70%) cases the samples were positive by PCR and could be sequenced. Out of all cases and contacts, a total of 153 serum and faecal samples were tested. HAV RNA was detected in 79 (52%) and 78 (99%) could be typed, which resulted in 40 unique sequences, 12 of which were detected in clusters of 2-14 cases. Since 2011, there seems to have been a slight, but steady increase in the fraction of HAV 1A strains (Figure 7.3.3), mostly originating from Morocco.

### 7.3.4 Research

Initially, the typing of IgM-positive samples by IDS was done for a period of two years, but is now being continued because 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.

The RIVM coordinated the HAV NET database, which was built to help identify the source of food-related clusters and outbreaks. As of 2015, 32 institutes from 27 countries all over the world have admission to the database and 18 institutes have actively submitted data. The HAV NET database currently contains a total of 6,935 sequences (HAV NET (N=2568) and Genbank (N=4367)) for the period 1957-2015. Data submitted by HAV NET partners include HAV strain sequences with additional information: case identification and immune status, possible transmission route (e.g. travel related), typed region and length of the fragment, geographic information of the sequence, and level of endemicity. In the HAV NET database, Genotype IA (60%) is the most prevalent; Genotype IB (19.5%) is more prevalent in Africa and the Middle East and Genotype IIIA (19.7%) is the most prevalent in Asia (India, Afghanistan). Available sequences have made it possible to identify and link outbreaks and their geographic origin internationally. The currently available HAV NET database contains information from most continents and genotypes, but resolution in some geographic areas is limited by the number and the length of sequences. It does, however, allow for estimating the most likely origin of the infecting strain in >90% of the cases.

### 7.3.5 International developments

Greece, Catalonia (Spain) and Israel reported an evaluation of the effect of routine vaccination against hepatitis A in children. Greece is the only European Union member state that in 2008 included hepatitis A vaccine in the routine national childhood immunisation programme. Mellou et al. [1] identified a decreasing trend in the HAV notification rate over the years 1982-2013. However, universal vaccination (~80% vaccine coverage of children) had no significant effect on the annual number of reported cases. In the last decade, one-third of all reported cases were Roma and, in 2013, three outbreaks including Roma cases were recorded. Contributing factors mentioned are a low vaccination coverage for this group, low socioeconomic conditions and poor hygiene. The authors suggest that universal vaccination may need to be reconsidered given the limited resources allocated to public health in Greece. Probably a more cost-effective approach would be to implement a programme that included: a) vaccination of high-risk groups, b) universal vaccination of Roma children and improving conditions at Roma camps, c) education of the population and travel advice, and d) enhancement of the control measures related to hepatitis A. In Catalonia, children have been vaccinated against hepatitis A at the age of 12 years since 1999 [2]. Attack rates declined and were as low as 1.5 per 100,000 inhabitants in the 2010-2013 period. Vaccine failures occurred at a very low rate. More striking was the increase of symptomatic infections among young children under 6 years of age. The authors hypothesize that genotype IIIA strains may produce more clinical cases in these young children than anticipated. They conclude that it would be better to vaccinate at an earlier age than is done now. In Israel, vaccination against hepatitis A was started in 1999 with a mean vaccine coverage of 92% for the first dose (given at 18 months of age) and 88% for the second dose (given at 24 months of age) [3]. In the pre-vaccination period (1993-1998), the average annual incidence was 50.4 per 100,000 inhabitants, which declined to an average of less than 1.0 per 100,000 inhabitants per year in 2008-2012. The

decrease was also seen in the unvaccinated populations. Of the cases reported between 2002 and 2012, 2% were reported to be vaccinated with one dose and less than 1% had received 2 doses (3 cases).

Espul et al. [4] reported the results of 5 years of follow-up of immune response after 1 or 2 doses of inactivated hepatitis A vaccine (Avaxim 80U Pediatric) given at 11-23 months of age in the Mendoza Province, Argentina. Most of the 411 children that were evaluable at year 5 had received 1 dose (n=318) and 85 had received 2 doses. Seroprotection after 5 years was 99.7% in the group with 1 dose and 100% in the group with 2 doses. The highest anti-HAV antibody concentrations were found in the children who had received 2 doses. The children who became seronegative received a booster dose. Results of an open Phase II study conducted at 2 centres in Belgium was published in 2015, reporting the immunogenicity of 2 doses of Epaxal® Junior compared with Epaxal® and Havrix® Junior in children 1-17 years, 5.5 years after the second dose [5]. Seroprotection at 5.5 years of follow-up was 100% for all 3 vaccines. GMCs were overall higher for Epaxal®. No statistically significant differences in GMCs were seen between Epaxal® Junior and Havrix® Junior. In addition, GMCs decreased more rapidly in younger children than in older children.

A study in Brazil involving 22 healthy adults and 20 outpatients with self-limited acute hepatitis A showed that the first vaccine dose induced HAV-specific cellular response similar to that found in an initial natural infection. [6]

Finally, Hens et al. [7] used the data from two clinical trials with results of hepatitis A vaccine-induced antibodies measured up to 17 years after the first dose to review the results of existing statistical models of the long-term persistence of antibodies. Based on these models and the available data, they predicted a duration of protection of at least 25 years in at least 95% of the vaccinees. These results are comparable to long-term estimates based upon shorter follow-up. The different models run by the authors were not consistent in the estimation of the maximum duration of protection, varying from a drop in protection after 25 years to protection of up to at least 40 years after vaccination.

### 7.3.6 Tables and Figures

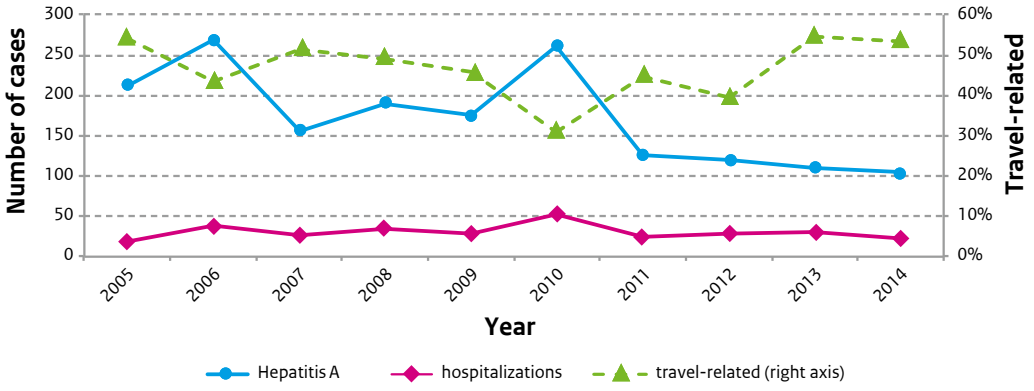


**Figure 7.3.1** Number of reported and hospitalised cases of hepatitis A and the percentage of travel-related cases, 2005-2014

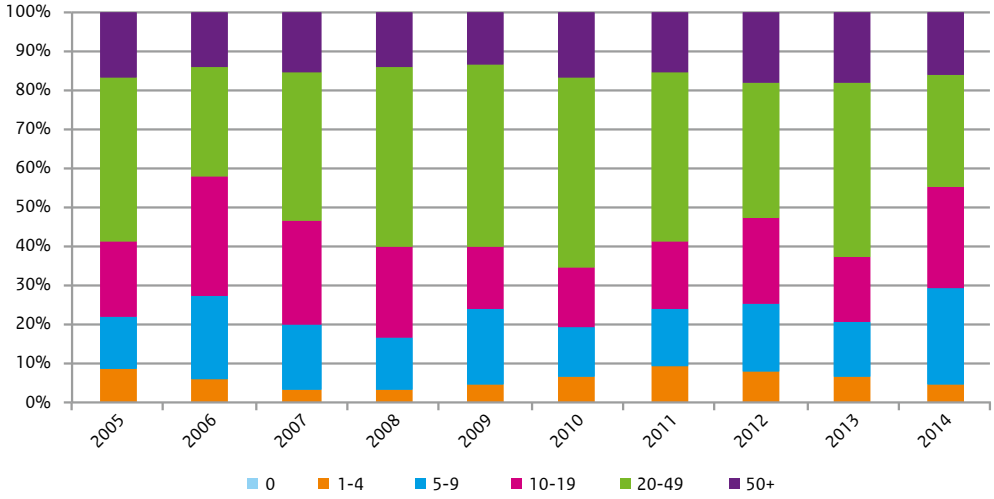


**Figure 7.3.2** Age distribution of notified hepatitis A cases, 2005-2014

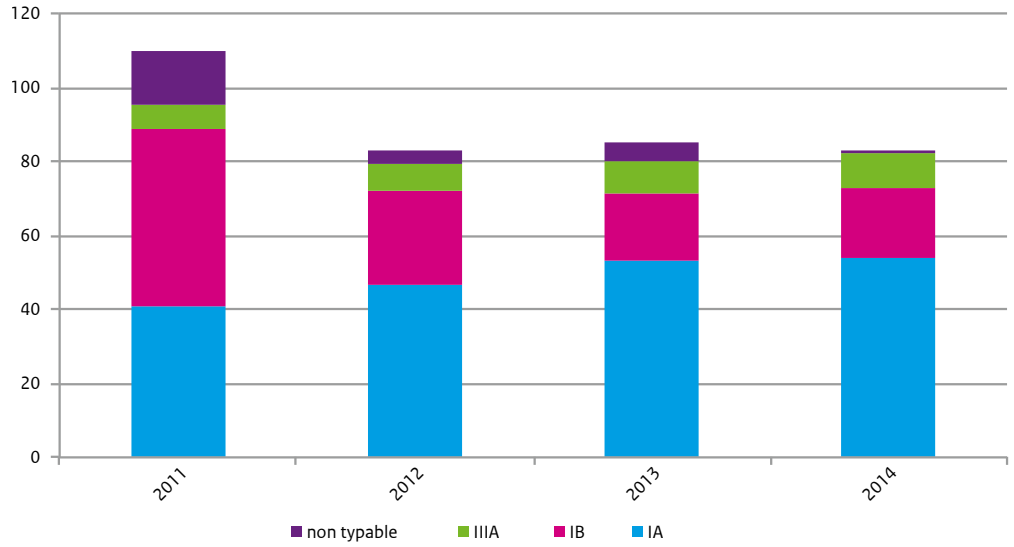


**Figure 7.3.3** HAV genotype distribution of HAV strains detected in the Netherlands in 2011-2014

## 7.3.7 Literature


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## 7.4 Meningococcal serogroup B disease

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### 7.4.1 Key points

- In 2014, a decrease in meningococcal serogroup B (MenB) disease was seen (60 cases in 2014, compared with 88 in 2013). In 2015, up to June, there were 32 MenB cases.
- In September 2015, UK babies born on or after 1 July 2015 will be offered the 4CMenB Bexsero® vaccine (at 2, 4 and 12 months of age) alongside their other routine immunisations.

### 7.4.2 Epidemiology

In 2014, 73% of all meningococcal cases were caused by MenB and 40% of the MenB disease cases concerned children younger than five years. From 2001 to 2012, the number of patients with meningococcal B disease decreased from 422 to 76. In 2013, a slight increase to 88 cases was observed, after which it decreased again to 60 cases in 2014. In 2015, up to June, there were 32 MenB cases. The incidence among 0-4 year-olds and 40-64 year-olds had decreased from 3.9 per 100,000 to 2.7 per 100,000 and from 0.3 per 100,000 to 0.1 per 100,000 in 2013 and 2014, respectively. The incidence among 5-9 year-olds increased from 0.6 per 100,000 in 2013 to 0.9 per 100,000 in 2014 (Figure 7.4.1).

### 7.4.3 Pathogen

Among others, Bijlsma et al. (2014) [1] described the epidemiology of PorA serosubtypes of serogroup B invasive meningococcal cases for the period 1960 to 2012. The most common PorA serosubtype during the first decade of the hyper-endemic period (1982-91) was P1.4, followed by P1.16 and P1.2. During the second decade (1992-2001), the most common serosubtypes were P1.4, P1.10 and P1.16. PorA finetype was available during the last decade (2002-2012), the most common finetypes were P1.7-2,4, P1.22,14 and P1.5-2,10.

### 7.4.4 Research

A large carriage study was conducted in the Netherlands during the epidemiological years (from July 1st to June 30th) 2013 and 2014. The preliminary results of this study showed an overall carriage prevalence of 16% in adolescents and young adults aged 13-22 years and serogroup B was the most frequently carried serogroup (27%).

### 7.4.5 International developments

In March 2015, it was announced that all babies in the UK will soon be vaccinated against MenB disease as part of the national childhood immunisation programme using the 4CMenB vaccine, Bexsero®.
In September 2015, UK babies born on or after 1 July 2015 will be offered the vaccine alongside their other routine immunisations (*http://www.meningitis.org/menb-vaccine*). In addition, babies born between 1 May and 31 May 2015 will be offered the 4CMenB vaccine at 4 and 12 months

and babies born between 1 June and 30 June 2015 will be offered the 4CMenB vaccine at 3, 4 and 12 months (*http://www.immunisationscotland.org.uk/vaccines-and-diseases/menb.aspx#menbcatchup*). The National Immunisation Advisory Committee (NIAC) in Ireland has recommended that the 4CMenB vaccine should be made routinely available to infants as part of the Primary Childhood Immunisation Schedule (subject to cost-effectiveness), but a decision has yet to be made by the Department of Health.
In the following countries there is a recommendation for 4CMenB vaccination for infants and children: Australia, Austria, Canada, the Czech Republic, Germany, Greece, Hungary, Italy, Poland, Portugal, Spain and the UK. In Canada and Portugal, there is also a recommendation for adolescents. No routine programme of 4CMenB in adolescents/young adults only has yet been implemented or announced [2]. However, on February 26, 2015, the Advisory Committee on Immunization Practices (ACIP) in the USA recommended the use of 4CMenB vaccines among certain groups of persons aged ≥10 years who are at increased risk for serogroup B meningococcal disease (*http://www.cdc.gov/mmwr/ preview/mmwrhtml/mm6422a3.htm*). In the USA, two meningococcal serogroup B vaccines have been licensed, i.e. Bexsero® and Trumenba® (Pfizer, containing two variants of the outer membrane lipoprotein factor H binding protein (FHbp, also referred as rLP2086 in this vaccine)), both for use in individuals aged 10-25 years old (and thus not for infants). In Europe, only Bexsero® has been licensed, where it is indicated for individuals aged 2 months and older (thus including infants).

Read and colleagues [3] reported a phase 3, observer-blind, randomised, controlled trial that assessed the effects on the carriage of meningococci in 2,954 students (aged 18-24 years). The students received two doses of 4CMenB, one dose of MenACWY-CRM, plus one dose of placebo, or two doses of Japanese encephalitis virus vaccine (control vaccine) in a 1:1:1 ratio, followed-up for 12 months. For both vaccines, significantly lower carriage prevalence were recorded versus the control group for any *N. meningitidis* strain. Although 4CMenB is characterised as a MenB vaccine, antigens in the vaccine are also present and able to induce bactericidal antibodies against non-serogroup B strains as well. No impact of 4CMenB only on capsular group B strains was observed. This may be due to the low number of capsular group B carriage acquisitions during the study, in addition to the observation that most acquisition events occurred after the first vaccine dose and before the second.

The potential coverage offered by the 4CMenB vaccine has been assessed retrospectively during MenB outbreaks worldwide since the mid-1970s [4]. Four hyper invasive lineages (CC32, CC41/44, CC269 and CC162) have dominated during outbreaks of serogroup B invasive meningococcal disease worldwide since the 1970s. For the 21 isolates from these four clonal complexes evaluated using both human Serum Bactericidal Assay and the Meningococcal Antigen Testing System (MATS), the coverage ranged from 67% (2/3 strains belonging to CC269) to 100% (8/8 strains belonging to CC32, 9/9 strains belonging to CC41/44 and 1/1 strain belonging to CC162).

Ladhani et al. [5] studied the potential use of the 4CMenB vaccine in addition to antibiotic chemoprophylaxis for preventing secondary cases. They estimated the numbers needed to vaccinate (NNV) with the 4CMenB vaccine to prevent a secondary case in household and

educational settings. Most secondary cases occur within a few days of diagnosis in the index case. Unlike conjugate vaccines, early protection offered after a single dose of the 4CMenB vaccine is likely to be low, particularly in young children, who are at a higher risk of secondary infection. The NNV is dependent on predicted meningococcal strain coverage, estimated onset of protection after one 4CMenB vaccine dose and estimated vaccine efficacy. In the most favourable scenario, in which they assumed the vaccine is administered within 4 days of the index case and prevents 90% of cases occurring after 14 days, the NNV for household contacts was more than 1,000. The NNV in educational settings was much higher. The authors concluded that the 4CMenB vaccine may have a protective role only in clusters and outbreaks and would not prevent secondary cases of index cases in household or educational settings.

McIntosh et al. [6] reviewed all 4CMenB studies. The studies found 4CMenB to be highly immunogenic, inducing protective antibody levels against serogroup B strains expressing vaccine antigens in >95% of vaccinated cohorts. When antibody levels waned, all tested groups (infants, toddlers, adolescents and adults) demonstrated booster responses. The MATS technique predicts that global coverage of 4CMenB against all serogroup B strains is in the range of 66% (Canada) to 91% (USA). Regarding the safety profile, local and systemic reactions and, notably, fever in infants increased following concomitant administration of 4CMenB with routine vaccines. Prophylactic paracetamol significantly decreased the frequency and severity of reactions in infants, with no clinically significant impact on the immunogenicity of 4CMenB or concomitant routine vaccines.

Rollier et al. [7] presented immunogenicity and safety data, which was published in peer-reviewed literature between 2004 and 2014, in the context of the recent recommendation for the use of the 4CMenB vaccine in infants in the UK. Despite the wealth of data on 4CMenB (already summarized in the paragraphs above), they also discussed the fact that a number of questions remain unanswered. It is not clear whether this vaccine will include herd protection. To provide this critical information, carriage studies should be conducted in all populations where the vaccine is introduced. Furthermore, vaccine effectiveness in the field is unknown. The vaccine will protect against strains that express sufficient levels of the specific variants of the vaccine antigens on the surface, but protection against other strains is not known. Carefully conducted surveillance post-vaccine implementation is needed. As this vaccine will not eliminate all capsular group B meningococcal disease, it is important that research into improved meningococcal vaccines continues. Currently, another vaccine with a potential to provide broad protection is in clinical development: a MenABCWY conjugate vaccine combining 4CMenB with the MenACWY conjugate vaccine, which is in a Phase II clinical trial.

In a review, Esposito et al. [8] discussed the immunogenicity, safety and tolerability of the 4CMenB vaccine in infants and toddlers, and the efficacy of different vaccination strategies. They state that, with the availability of the bivalent rLP2086 vaccine (Trumenba®) for the adolescent age, it will be important to compare vaccination strategies that cover different age groups and to understand the impact of the two vaccines against IMD overall, meningococcal disease due to serogroups different from MenB and meningococcal carriage in the nasopharynx.

Medini et al. [9] described the public-private cooperation in which the MATS assay platform was made available to meningococcal reference laboratories. So 4CMenB coverage can be estimated in countries around the world. They also discuss the potential use of MATS for post-implementation surveillance.

### 7.4.6 Tables and Figures

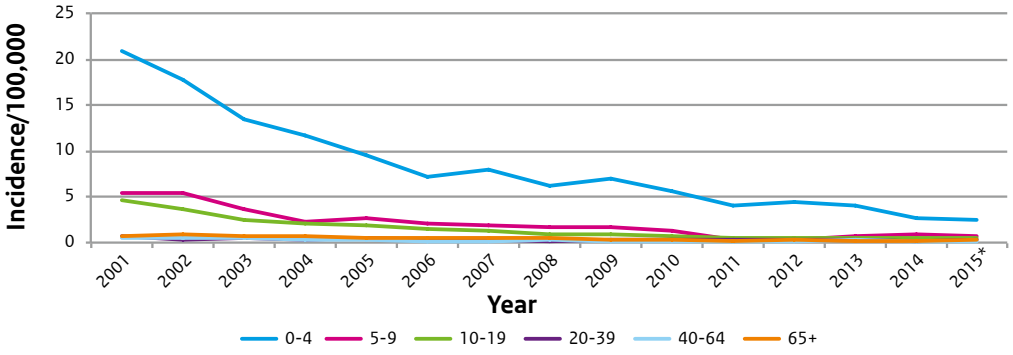


**Figure 7.4.1** Age-specific incidence of MenB disease, 2001-2015* (*up to June 2015)

Source: NRBM

**Table 7.4.1** Absolute numbers of invasive MenB isolates per age-category from 2001-2015* (*up to June 2015)

Source: NRBM

| Age in yrs | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **0-4** | 210 | 180 | 137 | 120 | 96 | 70 | 77 | 59 | 65 | 52 | 37 | 41 | 36 | 24 | 12 |
| **5-9** | 54 | 53 | 36 | 22 | 27 | 20 | 18 | 17 | 17 | 12 | 3 | 3 | 6 | 8 | 3 |
| **10-19** | 88 | 72 | 49 | 40 | 38 | 28 | 27 | 17 | 18 | 13 | 10 | 10 | 11 | 9 | 6 |
| **20-39** | 32 | 19 | 27 | 12 | 20 | 16 | 14 | 7 | 11 | 13 | 10 | 9 | 12 | 6 | 5 |
| **40-64** | 24 | 31 | 28 | 22 | 16 | 11 | 11 | 15 | 7 | 12 | 10 | 6 | 17 | 8 | 1 |
| **65+** | 14 | 20 | 16 | 15 | 12 | 10 | 12 | 13 | 8 | 10 | 5 | 7 | 6 | 5 | 5 |
| Total | 422 | 375 | 293 | 231 | 209 | 155 | 159 | 128 | 126 | 112 | 75 | 76 | 88 | 60 | 32 |

### 7.4.7 Literature


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## 7.5 Meningococcal non-serogroup B and C types

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### 7.5.1 Key points

- In 2014, 19 (23%) meningococcal cases were caused by non-serogroup B or C types out of a total of 83 cases. In 2015, up to June, 10 out of 45 cases were caused by non-serogroup B or C types.
- Most non B and C meningococcal cases were caused by serogroup Y, with 12 and 5 cases in 2014 and 2015, respectively, up to June.
- In March 2015, the British JCVI (Joint Committee on Vaccination and Immunisation) advised offering a MenACWY conjugate vaccine to 13-18 year-olds due to a continuous rise in cases of MenW since 2009.

### 7.5.2 Epidemiology

#### *7.5.2.1 Meningococcal serogroup W*

Since 2001, the number of meningococcal serogroup W (MenW) cases decreased to 1-7 cases each year. In 2014, the number of MenW cases amounted to 2 and in 2015, up to June, there were 4 MenW cases (Figure 7.5.1 and Table 7.5.1).

#### *7.5.2.2 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 2008 and 2009. From 2010 to 2014, the number of MenY cases ranged from 12 to 15 cases each year, with most cases (5 out of 12) occurring among individuals aged 65 years and older. In 2015, up to June, there were 5 MenY cases, four of which were in the age group 65+ (Figure 7.5.1 and Table 7.5.1).

#### *7.5.2.3 Other meningococcal serogroups*

In 2014, one Men29E, one MenX and 2 non-groupable Men were reported. In 2015, up to June, no cases with a meningococcal serogroup other than MenW or MenY were reported.

### 7.5.3 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.

### 7.5.4 Research

As mentioned in the MenC chapter, a large prospective study was conducted to compare a MenCC and MenACWY conjugate booster vaccine 11 years after priming in healthy 10, 12 and 15 year-olds. This study also aims to investigate, for serogroup A, W and Y, possible differences in age in MenAWY-specific SBA titres at baseline, 1 month and 1 year after priming. Results are expected at the end of 2015.

### 7.5.5 International developments

Public Health England conducted enhanced national surveillance of invasive meningococcal disease in England and Wales [1]. Detailed clinical information was obtained for all laboratory-confirmed MenW cases diagnosed during 3 epidemiological years (2010-2011 to 2012-2013) and whole genome sequencing analysis of the clinical isolates was performed. A year-on-year increase in invasive MenW disease was shown across all age groups since 2009-2010, which was due to rapid endemic expansion of a single clone belonging to the sequence type 11 complex (cc11). In the 129 MenW cases diagnosed, most patients were previously healthy, had not travelled abroad prior to the illness and the majority of cases presented with septicaemia. Thirty-seven per cent required intensive care and 12% died. There was no association between the infecting strain, clinical disease or outcome.

By the end of May 2015, 170 MenW cases had been reported in the UK in the epidemiological year 2014/2015, compared with 88 and 46 cases for the same period in 2013/2014 and 2012/2013, respectively. MenW is responsible for 25% of all IMD cases in 2014/2015, compared with 15% in 2013/2014 and 7% in 2012/2013. Because of the continuing rapid increase in MenW disease, the UK Departments of Health announced a rapid introduction of an adolescent MenACWY conjugate vaccine programme to begin in August 2015. The adolescent MenC conjugate vaccine currently recommended for 13-14 year-olds will be replaced by the MenACWY conjugate vaccine [2].
Also, in some other European countries, a small increase in MenW disease has been noticed. In the Netherlands, the number of MenW cases has been consistently low since 2001 and there are no signs of an increase in the number of cases.

### 7.5.6 Tables and Figures

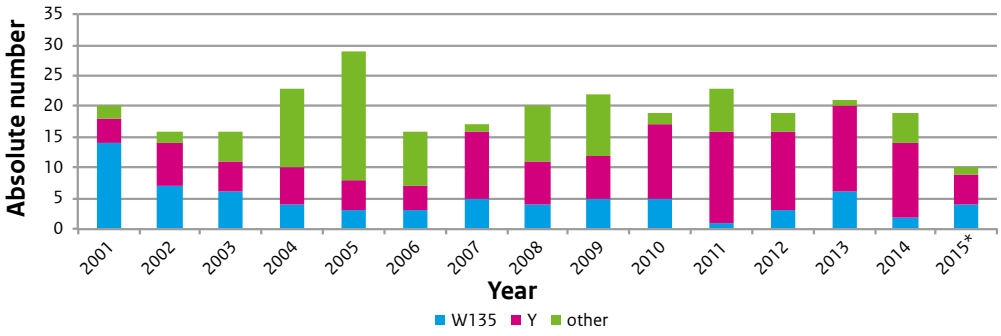


**Figure 7.5.1** Absolute number of meningococcal non-serogroup B or C isolates (e.g. A, 29E, W, X, Y, Z, non-groupable), 2001-2015*
(*up to June 2015)
Source: NRBM

**Table 7.5.1** Absolute number of invasive MenW isolates per age category, 2001-2015* (*up to June 2015)

Source: NRBM

| Age in yrs | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **0-4** | 5 | 1 | 3 | 0 | 1 | 2 | 2 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| **5-9** | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| **10-19** | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 0 |
| **20-39** | 4 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 |
| **40-64** | 3 | 2 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 2 | 2 |
| **65+** | 1 | 1 | 2 | 3 | 1 | 0 | 1 | 1 | 1 | 2 | 0 | 1 | 4 | 0 | 1 |
| Total | 14 | 7 | 6 | 4 | 3 | 3 | 5 | 4 | 5 | 5 | 1 | 3 | 6 | 2 | 4 |

**Table 7.5.2** Absolute number of invasive MenY isolates per age category, 2001-2015* (*up to June 2015)

Source: NRBM

| Age in yrs | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **0-4** | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 2 | 2 | 1 | 0 |
| **5-9** | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 3 | 0 | 1 | 0 |
| **10-19** | 0 | 1 | 1 | 2 | 0 | 0 | 1 | 0 | 0 | 2 | 5 | 1 | 1 | 2 | 0 |
| **20-39** | 1 | 2 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 3 | 2 | 2 | 0 | 2 | 0 |
| **40-64** | 1 | 0 | 1 | 1 | 2 | 0 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 1 | 1 |
| **65+** | 2 | 4 | 1 | 2 | 3 | 4 | 6 | 4 | 3 | 3 | 4 | 2 | 8 | 5 | 4 |
| Total | 4 | 7 | 5 | 6 | 5 | 4 | 11 | 7 | 7 | 12 | 15 | 13 | 14 | 12 | 5 |

## 7.5.7 Literature


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# 8
# Other possible future NIP candidates

*N.Y. Rots*

## 8.1 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 8.1. Relevant developments of combination vaccines are described in earlier chapters.

## 8.2 Tables and figures

**Table 8.1** 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 | Phase III,<br>FDA fast track designation |
| Helicobacter pylori | HP3 vaccine (Chiron/Novartis) | Phase I completed, limited protective immunity |
| Shigella | Live attenuated single-strain *Shigella* vaccine<br>Killed trivalent whole-cell vaccine, bioconjugate | Phase I |
| Staphylococcus Aureus | Staphylococcus Aureus Vaccine (SA4Ag) | Phase I promising data. Previous phases I-III with different vaccine candidates all failed, safety concerns and low efficacy |
| Streptococcus group A & B | Group A:<br>N-terminal M protein-based multivalent vaccines (26-valent and 30-valent vaccines)<br>Conserved M protein vaccines<br>Group B:<br>Trivalent vaccine | Phase II<br><br><br>Phase I<br>Phase I,<br>Phase II |
| Tuberculosis<br>(all forms all ages) | Whole-cell mycobacteria recombinant subunit vaccines | Phase II |

| Disease | Vaccine | Status |
|---|---|---|
| **Viral diseases** | | |
| Chikungunya | Live recombinant Measles Virus based vaccine<br>Virus-like particle vaccine | Phase I |
| Cytomegalovirus (CMV) | Glycoprotein B vaccine<br>DNA vaccine<br>live 'Towne' vaccine | Phases I and II |
| Ebola | rVSV-ZEBOV (Merck/ NewLink Genetics)<br>ChAd3-ZEBOV (GSK/PHAC)<br>Ad26-EBOV and MVA-EBOV (Johnson & Johnson and Bavarian Nordic)<br>Novavax | Phase III<br>Phase III<br>Phase II<br>Phase I |
| Epstein–Barr | Recombinant gp350 vaccine<br>Glycoprotein subunit vaccine | Phase II |
| Hepatitis E | Recombinant protein vaccine | Phase II |
| Herpes simplex | Glycoprotein subunit vaccines | Phases I-III |
| Marburg virus | DNA vaccine | Phase I |
| Middle East Respiratory Syndrome-coronavirus (MERS-CoV) | MVA-MERS-S | Phase I in preparation |
| Parainfluenza type I | Live attenuated vaccine | Phases I-II |
| Respiratory syncytial virus (RSV) | Live attenuated vaccines<br>Protein based vaccines<br>Gene-based vector vaccines | Phases I-II |
| Severe Acute Respiratory Syndrome (SARS) | Recombinant DNA plasmid vaccine | Phases I |
| West Nile Virus | Inactivated vaccine | Phase I |

Source: WHO and clinicaltrial.gov, Website pharmaceutical companies.

# List of abbreviations

| | |
|---|---|
| 4CMenB | multicomponent meningococcal B vaccine |
| ACIP | Advisory Committee on Immunisation Practices |
| AE | adverse events |
| AEFI | adverse events following immunisation |
| AFP | acute flaccid paralysis |
| aP | acellular pertussis |
| ASIA | autoimmune/inflammatory syndrome induced by adjuvants |
| BES | Bonaire, Sint Eustatius and Saba, the Dutch Caribbean |
| bOPV | bivalent oral polio vaccine |
| CAP | community acquired pneumonia |
| CBS | Statistics Netherlands |
| CC | clonal complex |
| CDC | Centres for Disease Control and Prevention |
| CFR | case-fatality rate |
| CI | confidence interval |
| CIb | Centre for Infectious Disease Control |
| CIN | Cervical intraepithelial neoplasia |
| CMR | Continuous Morbidity Registration |
| CMV | Cytomegalovirus |
| CSF | cerebrospinal fluid |
| CSI | Chlamydia trachomatis Screening and Implementation study |
| DA | Decision Aid |
| DALY | Disability Adjusted Life Years |
| DHD | Dutch Hospital data |
| DNA | desoxyribonucleic acid |
| dPLY | detoxified pneumolysin |
| DTaP | combination of diphtheria, tetanus and acellular pertussis vaccines |
| DTaP-IPV | combination of diphtheria, tetanus, acellular pertussis and inactivated polio vaccines |
| DT-IPV | combination of diphtheria, tetanus and inactivated polio vaccines |
| DTP | combination of diphtheria, tetanus and pertussis vaccines |
| DTpa | combined reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine |
| DTwP | combination of diphtheria, tetanus and whole-cell pertussis vaccines |
| DVP | Department for Vaccine Supply and Prevention Programmes |
| ECDC | European Centre for Disease Control and Prevention |
| ED | emergency department |
| EEA | European Economic Area |
| EIA | enzyme immunoassay |
| ELS | extensive limb swelling |
| EMA | European Medicines Agency |
| EPIS-VPD | the Epidemic Intelligence Information System for vaccine preventable diseases |
| EU | European Union |

| | |
|---|---|
| F | fusion |
| FDA | Food and Drug Administration |
| FHA | filamentous haemagglutinin |
| Fim2 | serotype 2 fimbriae |
| Fim3 | serotype 3 fimbriae |
| GAPIII | the WHO global action plan to minimize poliovirus facility-associated risk |
| GGD | Municipal Health Service |
| GMC | geometric mean IgG concentrations |
| GP | General Practitioner |
| GSK | Glaxo Smith Kline |
| GW | genital warts |
| HAV | hepatitis A virus |
| HAVANA | Study of HPV prevalence among young girls |
| HBO | higher vocational education |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HC | Health Council |
| HCSP | the French Council of Public Health |
| HCW | health care workers |
| HepB | hepatitis B virus |
| Hia | *Haemophilus influenzae* type a |
| Hib | *Haemophilus influenzae* type b |
| Hid | *Haemophilus influenzae* type d |
| Hie | *Haemophilus influenzae* type e |
| Hif | *Haemophilus influenzae* type f |
| Hib/MenC-TT | combined *Haemophilus influenzae* type b and Neisseria meningitidis serogroup C tetanus toxoid conjugate vaccine |
| HibMenCY-TT | Meningococcal groups C and Y and Haemophilus b tetanus toxoid conjugate vaccine |
| HIV | human immunodeficiency virus |
| HN | haemagglutinin-neuraminidase |
| HPA | Health Protection Agency |
| HPV | human papillomavirus |
| hrHPV | high-risk human papillomavirus |
| HTPP | hospital-treated primary pneumonia |
| HZ | herpes zoster |
| ICD | International Classification of Diseases |
| ICER | incremental cost-effectiveness ratio |
| ICPC | International Classification of Primary Care |
| ICU | intensive care unit |
| IDS | Centre for Infectious Disease Research, Diagnostics and Screening |
| IMD | invasive meningococcal disease |
| IPD | invasive pneumococcal disease |
| IPV | inactivated polio vaccine |

| | |
|---|---|
| IRR | incidence rate ratio |
| iVDPV | vaccine-derived polioviruses in immunocompromised children |
| JCVI | Joint Committee on Vaccination and Immunisation |
| LBZ | National Register Hospital care |
| LcM+PppA | pneumococcal protective protein A co-administrated with heat-killed-Lactobacillus casei |
| LINH | the Netherlands Information Network of General Practice |
| LMR | National Medical Registration |
| lrHPV | low-risk human papillomavirus |
| MATS | Meningococcal Antigen Typing System |
| MBO | intermediate vocational education |
| MCV | measles containing vaccine |
| Men29E | Meningococcal serogroup 29E |
| MenA | Meningococcal serogroup A |
| MENA | Middle East and North Africa |
| MenACWY-CRM | quadrivalent meningococcal CMR conjugate vaccine |
| MenACWY-D | quadrivalent meningococcal diphtheria toxoid conjugate vaccine |
| MenACWY-TT | tetravalent meningococcal tetanus toxoid conjugate vaccine |
| MenB | Meningococcal serogroup B |
| MenC | Meningococcal serogroup C |
| MenCC | Meningococcal conjugate vaccines |
| MenC-PS | Meningococcal serogroup C polysaccharide |
| MenC-TT | Meningococcal serogroup C polysaccharide-tetanus toxoid |
| MenW | Meningococcal serogroup W |
| MenX | Meningococcal serogroup X |
| MenY | Meningococcal serogroup Y |
| MenZ | Meningococcal serogroup Z |
| MERS-CoV | Middle East Respiratory Syndrome-coronavirus |
| MF | multiplication factor |
| MHS | Municipal Health Service (GGD) |
| MIA | multiplexed immuno assays based on Luminex technology |
| MML | Laboratories of Medical Microbiology |
| MMR | combination of measles, mumps and rubella vaccines |
| MMRV | combination of measles, mumps, rubella and Varicella vaccines |
| MSM | men who have sex with men |
| NB | non-bacteremic |
| NI | non-invasive |
| NI | non-inferiority |
| NIAC | National Immunisation Advisory Committee |
| NIP | national immunisation programme |
| NIVEL | Netherlands Institute for Health Services Research |
| NIVEL-PCD | NIVEL Primary Care Database |
| NKR | the Netherlands Cancer Registry |
| NNV | numbers needed to vaccinate |

| | |
|---|---|
| NPG | National Influenza Prevention Programme |
| NRBM | Netherlands Reference laboratory for Bacterial Meningitis |
| NREVSS | National Respiratory and Enteric Virus Surveillance System |
| NTHi | nontypeable *Haemophilus influenzae* strains |
| NVI | Netherlands Vaccine Institute |
| OMV | outer membrane vesicle |
| OPV | oral polio vaccine |
| OR | odds ratio |
| PASSYON | Papillomavirus Surveillance among STI clinic Youngsters |
| PCR | polymerase chain reaction |
| PCV | pneumococcal conjugate vaccine |
| PCV7-TT | heptavalent pneumococcal conjugate tetanus toxoid conjugate vaccine |
| PEP | post-exposure prophylaxis |
| PHiD-CV | 10-valent pneumococcal nontypeable Haemophilus influenza protein D conjugate vaccine |
| PhtD | pneumococcal histidine triad D |
| PIENTER | assessing immunisation effect to evaluate the NIP |
| Pneu | Pneumococcal vaccination |
| PPV | proportion of population vaccinated |
| PPSV23 | 23-valent pneumococcal polysaccharide vaccine |
| Prn | pertactin |
| PRN | plaque-reduction neutralisation test |
| PRP | polyribosyl-ribitol-phosphate |
| Ptx | pertussis toxin |
| QALY | quality-adjusted life year |
| RIVAR | multicentre study Risk-Group Infant Vaccination Against Rotavirus |
| RIVM | National Institute for Public Health and the Environment, the Netherlands |
| RNA | Ribonucleic acid |
| RR | relative risk |
| RSV | respiratory syncytial virus |
| RT | real-time |
| RV | Rotavirus |
| SAGE | Strategic Advisory Group of Experts |
| SARS | Severe Acute Respiratory Syndrome |
| SBA | serum bactericidal antibody |
| SH | small hydrophobic |
| SP-MSD | Sanofi Pasteur MSD |
| SSA | Sub-Saharan Africa |
| SSPE | subacute sclerosing panencephalitis |
| STI | sexually transmitted infections |
| SUR | Surinam, Netherlands Antilles and Aruba |
| SVIM | a 'screen, vaccinate or initiate management' strategy |
| Tdap | tetanus, diphtheria and pertussis vaccine |
| T-PEP | tetanus post-exposure prophylaxis |

| | |
|---|---|
| TQS | a bedside test for tetanus immunity |
| TT | tetanus toxoid |
| VDPV | Vaccine-derived polio virus |
| VE | vaccine effectiveness |
| VLP | virus-like particle |
| VO | a 'vaccinate only' strategy |
| VPD | vaccine-preventable disease |
| VT-CAP | vaccine-type pneumococcal community acquired pneumonia |
| VT-IPD | vaccine-type invasive pneumococcal disease |
| VZV | varicella zoster virus |
| VWS | Ministry of Health, Welfare and Sport |
| WHO | World Health Organization |
| WIV | Belgian Scientific Institute of Public Health |
| wP | whole-cell pertussis |
| WPV | wild polio virus |
| YLD | Years Lived with Disability |
| YLL | Years of Life Lost |

# Appendix

# 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 that 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. Since statistical year 2013, the data of CBS will use IRIS for automatic coding for cause of death. One of the advantages is the increase of international comparison of the figures. The change in coding will cause (once-only) considerable shifts in the statistics. Data for 2013 and 2014 are still preliminary.

### Morbidity data

*Notifications*

Notifications by law are an important surveillance source for diseases included in the NIP. The 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 A1.1 for the period of notification for each disease [1]. In December 2008, a new law (Wet Publieke Gezondheid) 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.

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 under-reporting and delays in reporting [2]. In each of the last three categories, different intervention measures can be enforced to prevent the spread of the disease.

**Table A1.1** Periods and category of statutory notification for vaccine-preventable diseases (VPDs) included in the current National Immunisation Programme (NIP)

| Disease | Category | Periods of notification by legislation |
|---|---|---|
| Diphtheria | B1 | from 1872 onwards |
| Pertussis | B2 | from 1975 onwards |
| Tetanus | C | 1950-1999,<br>from December 2008 onwards |
| Poliomyelitis | A | from 1923 onwards |
| Invasive *Haemophilus influenzae* type b | C | from December 2008 onwards |
| Hepatitis B disease | B2 | from 1950 onwards |
| Invasive pneumococcal disease[a] | C | from December 2008 onwards |
| Mumps | C | 1975-1999,<br>from December 2008 onwards |
| Measles | B2 | 1872-1899,<br>from 1975 onwards |
| Rubella | B2 | from 1950 onwards |
| Invasive meningococcal disease | C | from 1905 onwards |

a For infants only.

*Hospital admissions*

Since 2013, the National Register Hospital Care (LBZ), managed by Dutch Hospital Data (DHD) 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-10 coding system.
Until 2010, hospital data was managed by the research institute Prismant in the National Medical Register (LMR); since 2011, DHD has managed the LMR. Up to 2012, discharge diagnoses were coded according to the ICD-9 coding system.
The coverage of this registration was about 99% until mid-2005. Thereafter, coverage has fluctuated due to changes in funding (see Table A1.2). Data presented in this report concerned only clinical admissions and were not corrected for changes in coverage.
Hospital admission data are also susceptible to under-reporting, as shown by De Greeff et al. in a paper on meningococcal disease incidence [3].

**Table A1.2** The completeness of LMR/LBZ over the years*, by day admissions and clinic admissions

| Year | Type of admission | Registered | Generated (=missing) |
|---|---|---|---|
| 2007 | Day admission | 87% | 13% |
| | Clinic admission | 89% | 11% |
| 2008 | Day admission | 88% | 12% |
| | Clinic admission | 88% | 12% |
| 2009 | Day admission | 87% | 13% |
| | Clinic admission | 88% | 12% |
| 2010 | Day admission | 86% | 14% |
| | Clinic admission | 89% | 11% |
| 2011 | Day admission | 79% | 21% |
| | Clinic admission | 85% | 15% |
| 2012 | Day admission | 72% | 28% |
| | Clinic admission | 82% | 18% |
| 2013 | Day admission | 74% | 26% |
| | Clinic admission | 84% | 16% |
| 2014** | Day admission | 82% | 18% |
| | Clinic admission | 99% | 1% |

* These numbers are an approximation of the exact percentage
Source: Statistics Netherlands (CBS) up to 2009 and Dutch Hospital Data (DHD) from 2010 onwards
** For 2014, the hospitalisation data are preliminary and incomplete.

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.

*Laboratory data*

Laboratory diagnostics are very important in monitoring infectious diseases and the effectiveness of vaccination; about 75% of all infectious diseases can be diagnosed only by laboratory tests [5]. However, limited information on patients is registered and, in many cases, laboratory confirmation is not sought for self-limiting VPDs. The different laboratory surveillance systems for diseases targeted by the NIP are outlined below.

*Netherlands Reference Laboratory Bacterial Meningitis*
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.

*Virological laboratories*
Each week, virological laboratories, which are part of the Dutch Working Group for Clinical Virology, send positive results of virological diagnostics to the RIVM. Approximately 22 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. Since the 1st of December 2014, information on the total number of tests done can be reported each week or by year.

*NIVEL Primary care database*
Incidence rates of varicella and herpes zoster in general practice were calculated using data from the routine electronic health records of general practitioners that are participating in Netherlands Institute for Health Services Research (NIVEL) Primary Care Database (NIVEL-PCD), which incorporates the former LINH (Landelijk Informatie Netwerk Huisartsenzorg) that is maintained at the 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 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 to report incidence rates using the new method starting in 2012 [8]. Due to the new estimation method, the data for 2012 (based on 219 practices) and onwards are not comparable to previous years.

### Burden of Disease

The composite health measure, the Disability Adjusted Life Year (DALY), has been developed to compare the impact of diseases. The idea behind this approach is that the impact of a particular disease can be divided into the number of years of life lost (i.e. premature mortality) and the number of years lived at less than full health (i.e. morbidity). The result is a single measurement unit that quantifies the years of healthy life lost due to a certain disease or infection. The full methodology used to estimate the disease burden of infectious diseases in the Netherlands expressed in DALYs is described in the State of Infectious Diseases in the Netherlands, 2013 [9, 10].

### Vaccine effectiveness

After the implementation of a vaccination in 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 [11].

## 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 ($N_{blood}$=10,128) [12] and in 2006–2007 ($N_{blood}$=7,904) [13]. The 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.
According to plan, a new survey will be conducted in 2016.

## 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 at the individual level (Præventis) [14].

## 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 [15].
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 the period before 2011 and the period running from 2011 onward should be made with caution. Furthermore, in 2011 Lareb started a campaign among parents of vaccinated children to promote the reporting of AEFIs. In 2014 the number of notifications declined by almost 20% compared with 2013 [16]. This is a worrying development. The medically trained perception and interpretation of a possible side effect is an essential link when it comes to the detection of new information about side effects. Therefore sufficient participation of health care providers in the reporting system for adverse events is important [16].
In addition, the Centre for Infectious Disease Control (CIb) of the RIVM conducts systematic studies to monitor the safety of the NIP, e.g. questionnaire surveys and linkage studies between different databases.

## Cost-effectiveness

The decision to include a certain vaccination option in the NIP is based on 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 NIP.

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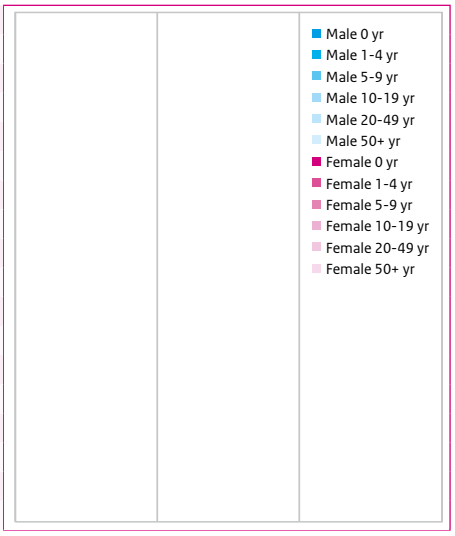
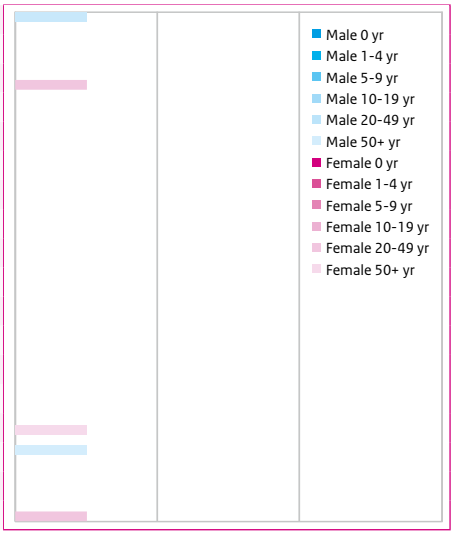
* RIVM publication

# Appendix 2 Morbidity and mortality figures

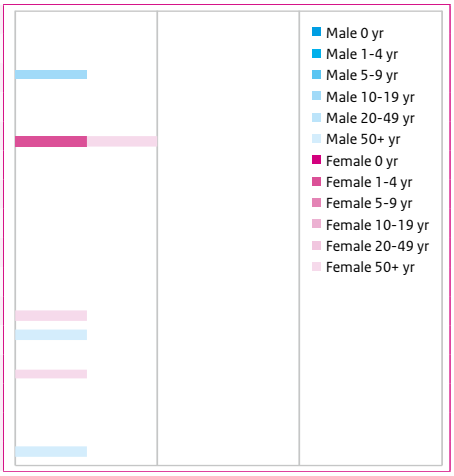
| Diphtheria | | | | | | | | ICD9: 032<br>ICD10: A36 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Mortality* | | | | | | | | |
| 1997 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 1998 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 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** | |
| 2013* | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 2014* | 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** | |
| 2014 | 0 | 0 | 0 | 0 | 1 | 0 | **1** | |

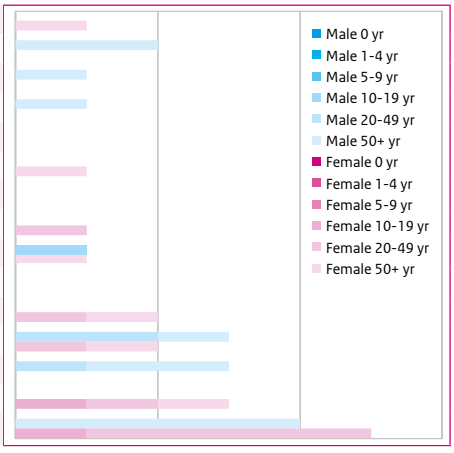



* Preliminary figures. Starting with statistical year 2013, the coding of causes of death is partly automatic.

| Diphtheria | | | | | | | | ICD9: 032<br>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** | |
| 2013 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 2014** | 0 | 0 | 0 | 0 | 0 | 1 | **1** | |
| *Laboratory diagnoses**** | | | | | | | | |
| 2000 | 0 | 0 | 0 | 0 | 0 | 1 | **1** | |
| 2001 | 0 | 0 | 0 | 0 | 0 | 2 | **2** | |
| 2002 | 0 | 0 | 0 | 0 | 0 | 1 | **1** | |
| 2003 | 0 | 0 | 0 | 0 | 0 | 1 | **1** | |
| 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 | 1 | 2 | **3** | |
| 2008 | 0 | 0 | 0 | 1 | 0 | 1 | **2** | |
| 2009 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 2010 | 0 | 0 | 0 | 0 | 1 | 1 | **2** | |
| 2011 | 0 | 0 | 0 | 0 | 3 | 2 | **5** | |
| 2012 | 0 | 0 | 0 | 0 | 2 | 2 | **4** | |
| 2013 | 0 | 0 | 0 | 1 | 3 | 1 | **5** | |
| 2014 | 0 | 0 | 0 | 1 | 4 | 5 | **10** | |



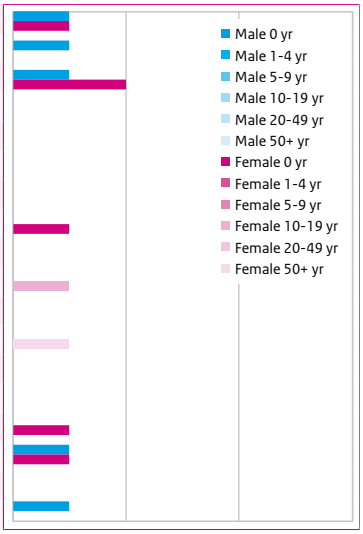



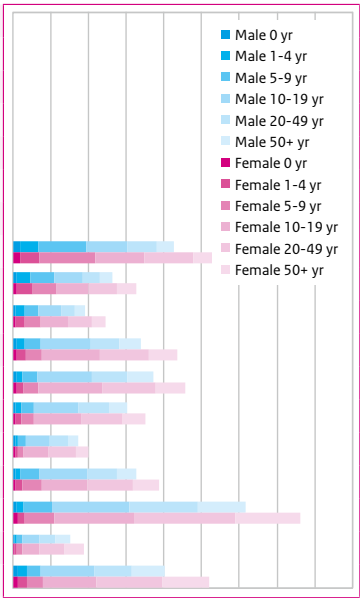

* Up to 2012, diseases are coded according to the ICD-9 coding system. Starting with 2013, diseases are coded according to the ICD-10 coding system.

** Preliminary and incomplete figures.

*** Number of diphtheria isolates.

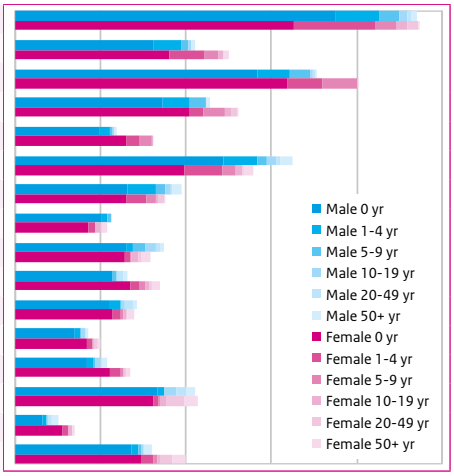
| Pertussis | | | | | | | | ICD9: 033<br>ICD10: A37 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Mortality* | | | | | | | | |
| 1997 | 2 | 0 | 0 | 0 | 0 | 0 | **2** | |
| 1998 | 1 | 0 | 0 | 0 | 0 | 0 | **1** | |
| 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** | |
| 2013* | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 2014* | 1 | 0 | 0 | 0 | 0 | 0 | **1** | |
| *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 | 1,054 | 931 | **3,405** | |
| 2014 | 258 | 490 | 788 | 2,858 | 2,719 | 2,137 | **9,250** | |



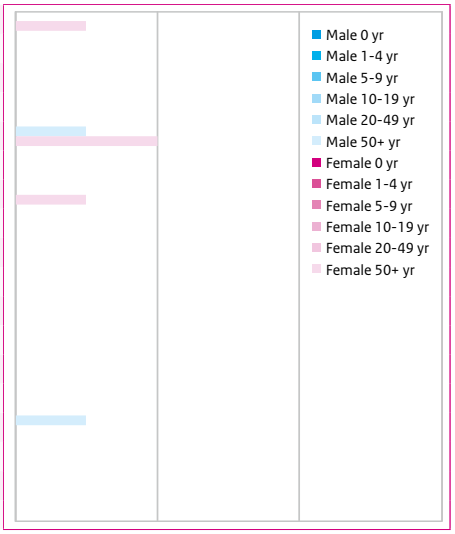

* Preliminary figures. Starting with statistical year 2013, the coding of causes of death is partly automatic.

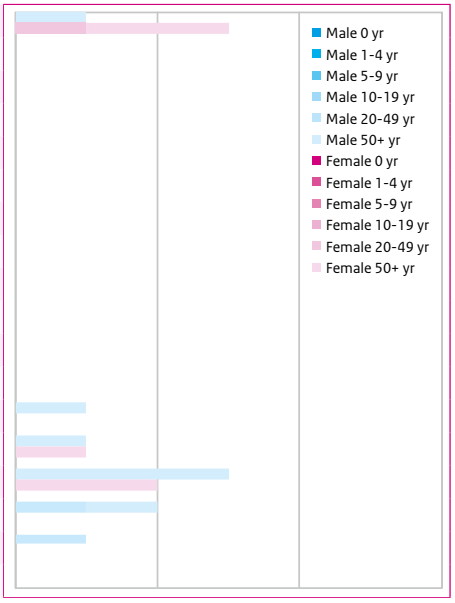
| Pertussis | | | | | | | | ICD9: 033<br>ICD10: A37 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Hospitalisations** | | | | | | | | |
| 1999 | 351 | 73 | 24 | 12 | 8 | 4 | **472** | |
| 2000 | 171 | 37 | 12 | 5 | 0 | 5 | **230** | |
| 2001 | 301 | 40 | 32 | 1 | 2 | 2 | **378** | |
| 2002 | 188 | 24 | 23 | 4 | 3 | 3 | **245** | |
| 2003 | 114 | 14 | 9 | 2 | 0 | 1 | **140** | |
| 2004 | 221 | 42 | 13 | 10 | 3 | 12 | **301** | |
| 2005 | 131 | 28 | 11 | 5 | 4 | 6 | **185** | |
| 2006 | 94 | 7 | 2 | 3 | 1 | 3 | **110** | |
| 2007 | 129 | 7 | 8 | 10 | 5 | 7 | **166** | |
| 2008 | 124 | 6 | 5 | 2 | 6 | 8 | **151** | |
| 2009 | 112 | 12 | 1 | 4 | 6 | 6 | **141** | |
| 2010 | 77 | 6 | 2 | 2 | 2 | 4 | **93** | |
| 2011 | 97 | 11 | 2 | 4 | 2 | 5 | **121** | |
| 2012 | 164 | 7 | 1 | 11 | 16 | 13 | **213** | |
| 2013 | 44 | 5 | 1 | 2 | 2 | 6 | **60** | |
| 2014** | 142 | 11 | 4 | 3 | 7 | 13 | **182** | |




* Up to 2012, diseases are coded according to the ICD-9 coding system. Starting with 2013, diseases are coded according to the ICD-10 coding system.
* For 3 patients, the age is unknown.
** Preliminary and incomplete figures.

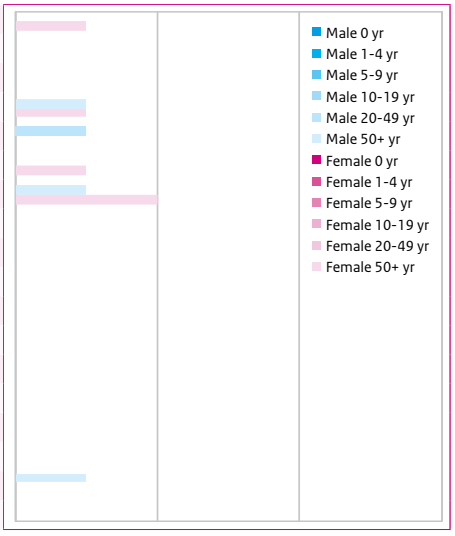
| Tetanus | | | | | | | | ICD9: 037, 7713<br>ID10: A33-35 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Mortality* | | | | | | | | |
| 1997 | 0 | 0 | 0 | 0 | 0 | 1 | **1** | |
| 1998 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 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** | |
| 2013* | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 2014* | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| *Notifications* | | | | | | | | |
| 1997 | 0 | 0 | 0 | 0 | 1 | 4 | **5** | |
| 1998 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 1999** | - | - | - | - | - | - | **-** | |
| 2000** | - | - | - | - | - | - | **-** | |
| 2001** | - | - | - | - | - | - | **-** | |
| 2002** | - | - | - | - | - | - | **-** | |
| 2003** | - | - | - | - | - | - | **-** | |
| 2004** | - | - | - | - | - | - | **-** | |
| 2005** | - | - | - | - | - | - | **-** | |
| 2006** | - | - | - | - | - | - | **-** | |
| 2007** | - | - | - | - | - | - | **-** | |
| 2008** | - | - | - | - | - | - | **-** | |
| 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** | |
| 2014 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |

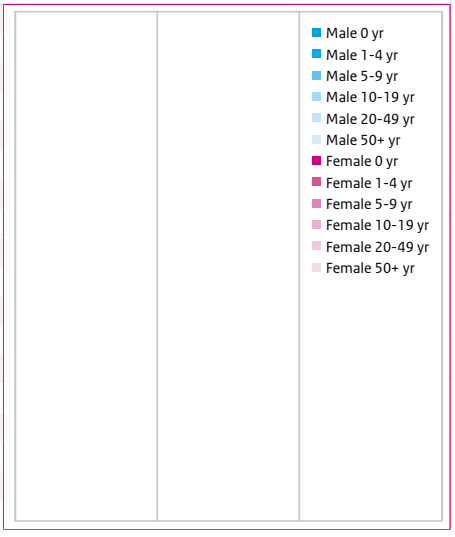



* Preliminary figures. Starting with statistical year 2013, the coding of causes of death is partly automatic.
** No notifications in 1999 to 2008.

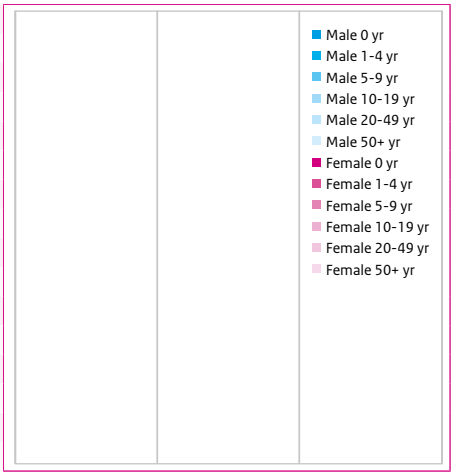
| Poliomyelitis | | | | | | | | ICD9: 045<br>ICD10: A80 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Mortality (acute)* | | | | | | | | |
| 1997 | 0 | 0 | 0 | 0 | 0 | 1 | **1** | |
| 1998 | 0 | 0 | 0 | 0 | 0 | 0 | **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** | |
| 2013* | 0 | 0 | 0 | 0 | 0 | 1 | **1** | |
| 2014* | 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** | |
| 2014 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |




* Preliminary figures. Starting with statistical year 2013, the coding of causes of death is partly automatic.

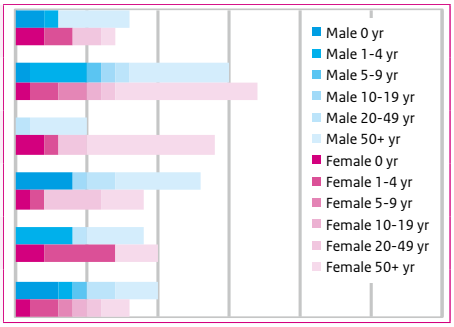
| Poliomyelitis | | | | | | | | ICD9: 045<br>ICD10: A80 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Hospitalisations** | | | | | | | | |
| 1999 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 2000 | 0 | 0 | 0 | 0 | 0 | 0 | **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** | |
| 2013 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 2014** | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |

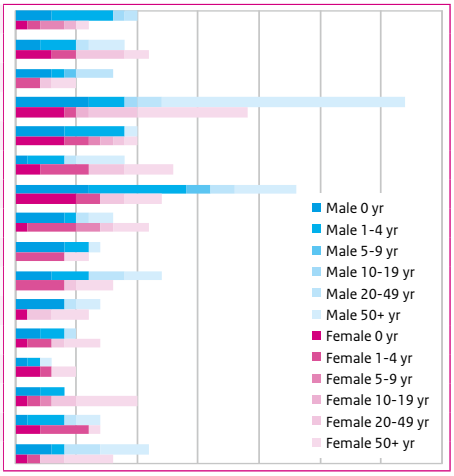



* Up to 2012, diseases are coded according to the ICD-9 coding system. Starting with 2013, diseases are coded according to the ICD-10 coding system.

** Preliminary and incomplete figures.

| ***Haemophilus influenzae* type b** | | | | | | | | **ICD9: 3200**<br>**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** | |
| 2014 | 4 | 3 | 2 | 1 | 3 | 5 | **18** | |
| *Hospitalisation (all types)*** | | | | | | | | |
| 1999 | 4 | 6 | 2 | 2 | 1 | 1 | **16** | |
| 2000 | 5 | 5 | 0 | 0 | 5 | 5 | **20** | |
| 2001 | 3 | 3 | 1 | 0 | 4 | 2 | **14** | |
| 2002 | 10 | 4 | 0 | 2 | 6 | 29 | **51** | |
| 2003 | 8 | 7 | 1 | 1 | 1 | 2 | **20** | |
| 2004 | 3 | 7 | 0 | 0 | 4 | 8 | **22** | |
| 2005 | 11 | 10 | 2 | 0 | 4 | 8 | **35** | |
| 2006 | 5 | 5 | 2 | 0 | 2 | 5 | **19** | |
| 2007 | 4 | 6 | 0 | 0 | 0 | 3 | **13** | |
| 2008 | 3 | 7 | 0 | 0 | 4 | 6 | **20** | |
| 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** | |
| 2013 | 3 | 7 | 0 | 0 | 1 | 3 | **14** | |
| 2014*** | 4 | 2 | 0 | 0 | 5 | 8 | **19** | |



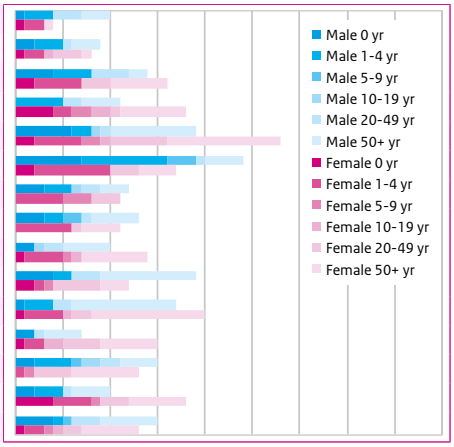

* Notifiable since 2009

** Up to 2012, diseases are coded according to the ICD-9 coding system. Starting with 2013, diseases are coded according to the ICD-10 coding system.

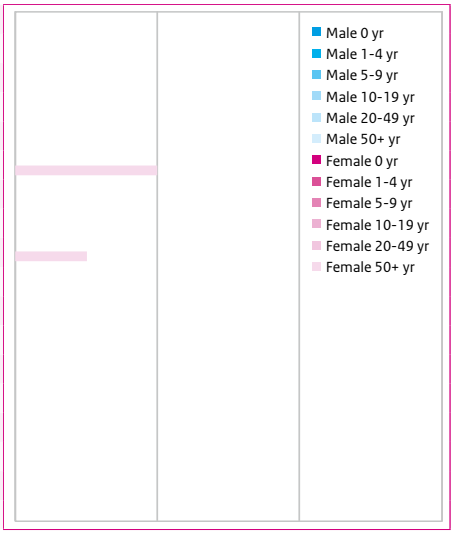
** For one patient, the age is unknown.

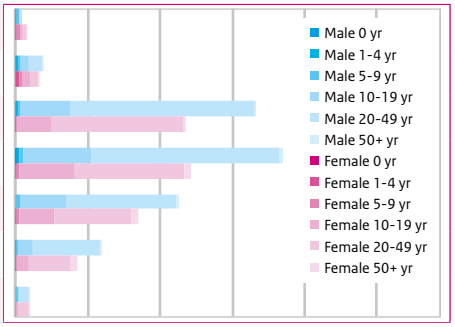
*** Preliminary and incomplete figures.

| *Haemophilus influenzae* type b | | | | | | | | ICD9: 3200<br>ICD10: A41.5, G00.0 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Isolates* | | | | | | | | |
| 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** | |
| 2014 | 5 | 3 | 2 | 1 | 6 | 12 | **29** | |



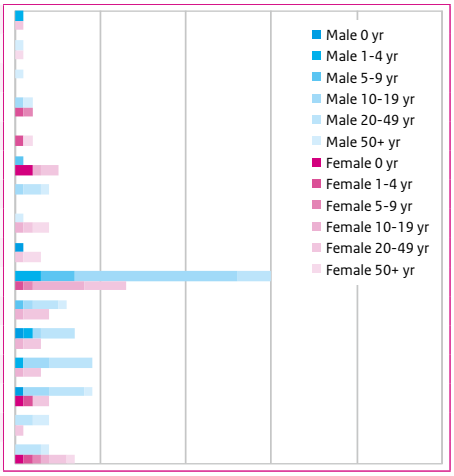
| Mumps | | | | | | | | ICD9: 072<br>ICD10: B26 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Mortality* | | | | | | | | |
| 1997 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 1998 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 1999 | 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** | |
| 2013* | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 2014* | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| *Notifications* | | | | | | | | |
| 2008** | 0 | 2 | 10 | 5 | 7 | 1 | **25** | |
| 2009 | 0 | 9 | 8 | 22 | 30 | 2 | **71** | |
| 2010 | 0 | 4 | 5 | 119 | 435 | 6 | **569** | |
| 2011 | 1 | 6 | 10 | 169 | 412 | 15 | **613** | |
| 2012 | 0 | 2 | 12 | 110 | 260 | 13 | **397** | |
| 2013 | 0 | 3 | 2 | 37 | 152 | 11 | **205** | |
| 2014 | 0 | 0 | 4 | 5 | 28 | 2 | **39** | |

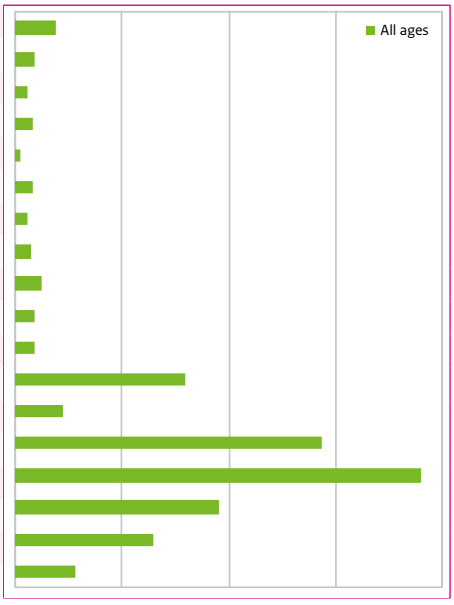



* Preliminary figures. Starting with statistical year 2013, the coding of causes of death is partly automatic.
** No notifications between 1 April 1999 and 31 December 2008

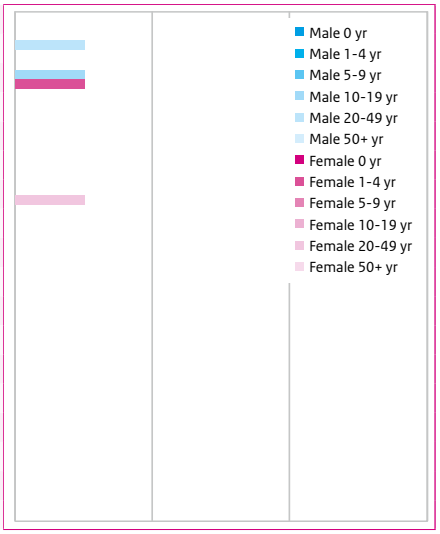
| Mumps | | | | | | | | ICD9: 072<br>ICD10: B26 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Hospitalisations** | | | | | | | | |
| 1999 | 0 | 1 | 0 | 0 | 1 | 0 | **2** | |
| 2000 | 0 | 0 | 0 | 0 | 0 | 2 | **2** | |
| 2001 | 0 | 0 | 0 | 0 | 0 | 1 | **1** | |
| 2002 | 0 | 1 | 1 | 1 | 0 | 1 | **4** | |
| 2003 | 0 | 1 | 0 | 0 | 0 | 1 | **2** | |
| 2004 | 2 | 0 | 1 | 1 | 2 | 0 | **6** | |
| 2005 | 0 | 0 | 0 | 1 | 2 | 1 | **4** | |
| 2006 | 0 | 0 | 0 | 1 | 1 | 3 | **5** | |
| 2007 | 1 | 0 | 0 | 0 | 1 | 2 | **4** | |
| 2008 | 0 | 4 | 5 | 25 | 9 | 0 | **43** | |
| 2009 | 0 | 0 | 1 | 2 | 6 | 1 | **10** | |
| 2010 | 1 | 1 | 0 | 2 | 6 | 0 | **10** | |
| 2011 | 0 | 1 | 0 | 4 | 7 | 0 | **12** | |
| 2012 | 2 | 1 | 0 | 3 | 6 | 1 | **14** | |
| 2013 | 0 | 0 | 0 | 0 | 3 | 2 | **5** | |
| 2014** | 1 | 1 | 1 | 1 | 5 | 2 | **11** | |
| *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** | |
| 2014 | - | - | - | - | - | - | **28** | |

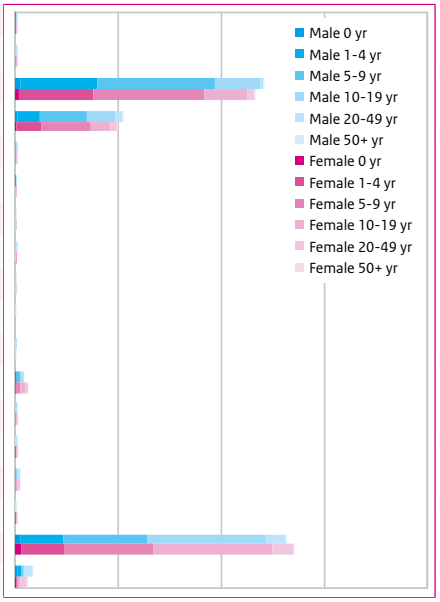



* Up to 2012, diseases are coded according to the ICD-9 coding system. Starting with 2013, diseases are coded according to the ICD-10 coding system.
* For 1 patient, the age is unknown.
** Preliminary and incomplete figures.

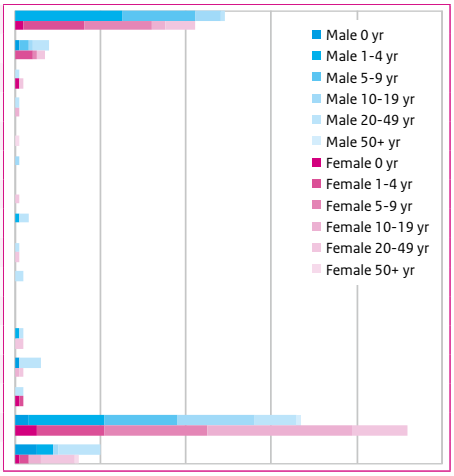
| Measles | | | | | | | | ICD9: 055<br>ICD10: B05 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Mortality* | | | | | | | | |
| 1997 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 1998 | 0 | 0 | 0 | 0 | 1 | 0 | **1** | |
| 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** | |
| 2013* | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 2014* | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| *Notifications* | | | | | | | | |
| 1997 | 1 | 9 | 0 | 0 | 11 | 0 | **21** | |
| 1998 | 1 | 1 | 2 | 2 | 3 | 0 | **9** | |
| 1999 | 41 | 738 | 1112 | 427 | 44 | 2 | **2,364** | |
| 2000 | 19 | 225 | 469 | 237 | 64 | 3 | **1,017** | |
| 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 | 1 | 1 | 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 | 8 | 0 | **9** | |
| 2008 | 4 | 8 | 38 | 39 | 21 | 0 | **110** | |
| 2009 | 1 | 2 | 2 | 3 | 7 | 0 | **15** | |
| 2010 | 1 | 2 | 2 | 1 | 9 | 0 | **15** | |
| 2011 | 2 | 2 | 7 | 14 | 26 | 0 | **51** | |
| 2012 | 1 | 2 | 0 | 1 | 6 | 0 | **10** | |
| 2013 | 53 | 425 | 840 | 1162 | 199 | 9 | **2,688** | |
| 2014 | 20 | 26 | 6 | 19 | 66 | 3 | **140** | |

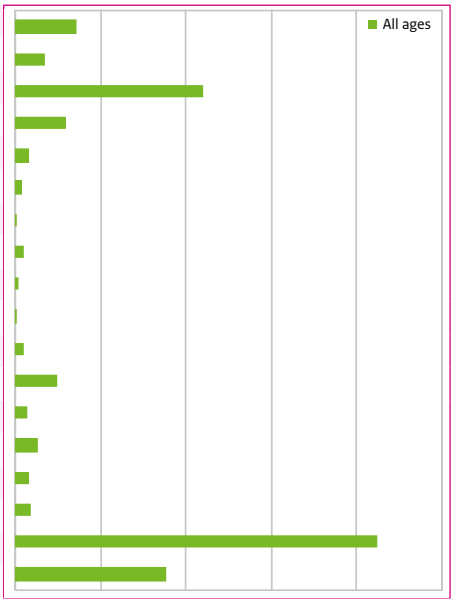



* Preliminary figures. Starting with statistical year 2013, the coding of causes of death is partly automatic.

| Measles | | | | | | | | ICD9: 055<br>ICD10: B05 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Hospitalisations** | | | | | | | | |
| 1999 | 2 | 39 | 33 | 9 | 8 | 0 | **91** | |
| 2000 | 1 | 4 | 3 | 1 | 6 | 0 | **15** | |
| 2001 | 1 | 0 | 0 | 0 | 2 | 0 | **3** | |
| 2002 | 0 | 0 | 0 | 1 | 1 | 0 | **2** | |
| 2003 | 0 | 0 | 0 | 0 | 0 | 1 | **1** | |
| 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** | |
| 2013 | 8 | 34 | 41 | 52 | 23 | 1 | **164** | |
| 2014** | 6 | 6 | 0 | 4 | 18 | 1 | **35** | |
| *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** | |
| 2014 | - | - | - | - | - | - | **88** | |



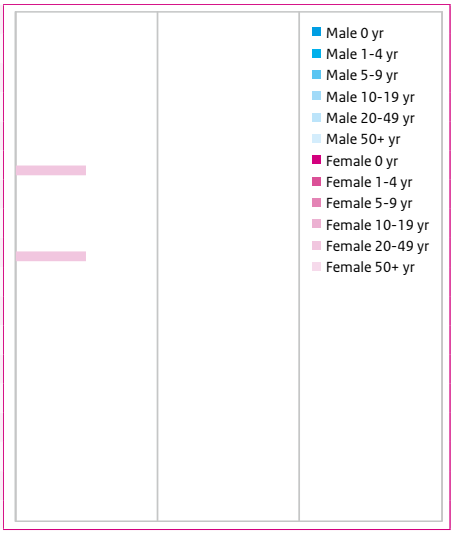



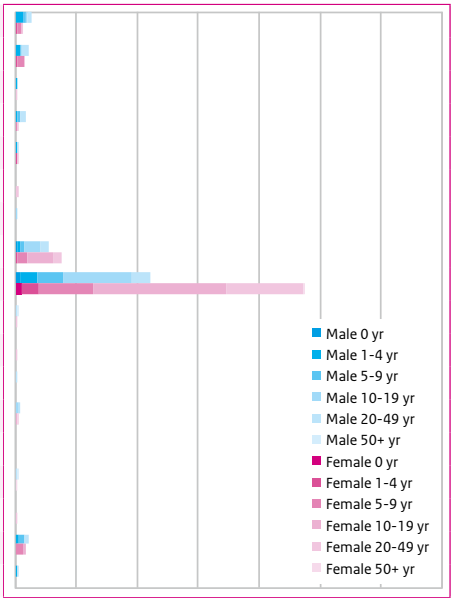

* Up to 2012, diseases are coded according to the ICD-9 coding system. Starting with 2013, diseases are coded according to the ICD-10 coding system.

* For 6 patients, the age is unknown.

** Preliminary and incomplete figures.

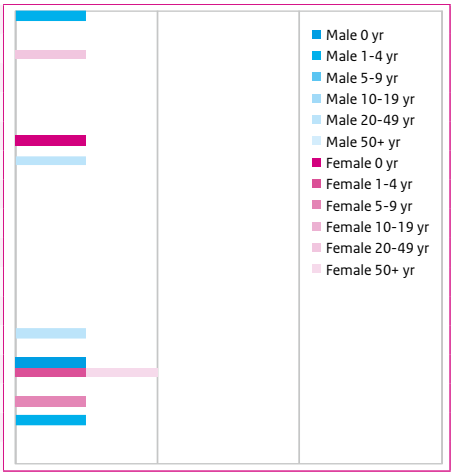
| Rubella (Acquired) | | | | | | | | ICD9: 056<br>ICD10: B06 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Mortality* | | | | | | | | |
| 1997 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 1998 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 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** | |
| 2013* | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 2014* | 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 | 2 | 4 | 12 | 33 | 14 | 0 | **65** | |
| 2005 | 9 | 28 | 66 | 166 | 78 | 2 | **349** | |
| 2006 | 0 | 0 | 0 | 0 | 4 | 1 | **5** | |
| 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 | 10 | 37 | 7 | 3 | 0 | **57** | |
| 2014 | 0 | 1 | 0 | 0 | 1 | 0 | **2** | |

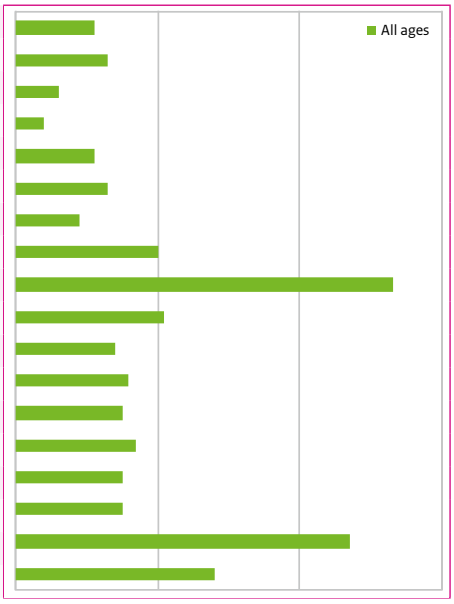



* Preliminary figures. Starting with statistical year 2013, the coding of causes of death is partly automatic.

| Rubella (Acquired) | | | | | | | | ICD9: 056<br>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 | 0 | **0** | |
| 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 | 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 | 1 | 0 | **1** | |
| 2011 | 1 | 1 | 0 | 0 | 0 | 1 | **3** | |
| 2012 | 0 | 0 | 1 | 0 | 0 | 0 | **1** | |
| 2013 | 0 | 1 | 0 | 0 | 0 | 0 | **1** | |
| 2014** | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| *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** | |
| 2014 | - | - | - | - | - | - | **28** | |

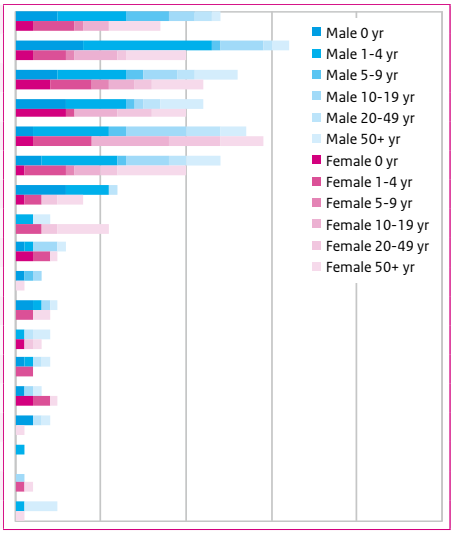


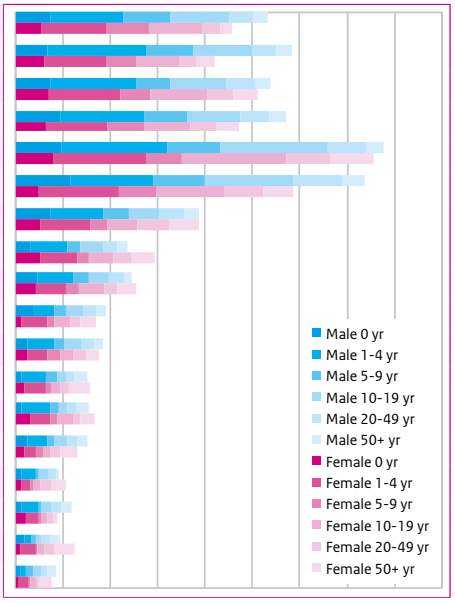




* Up to 2012, diseases are coded according to the ICD-9 coding system. Starting with 2013, diseases are coded according to the ICD-10 coding system.

** Preliminary and incomplete figures.

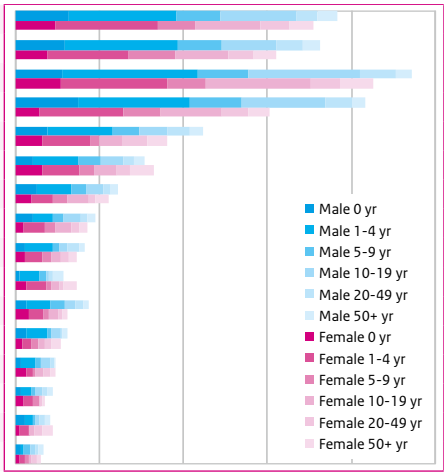
| Meningococcal disease | | | | | | | | ICD9: 036.0-4, 036.8-9<br>ICD10: A39 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Mortality* | | | | | | | | |
| 1997 | 7 | 13 | 6 | 6 | 2 | 7 | **41** | |
| 1998 | 10 | 19 | 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** | |
| 2013* | 0 | 1 | 0 | 1 | 0 | 1 | **3** | |
| 2014* | 0 | 1 | 0 | 0 | 0 | 5 | **6** | |
| *Notifications* | | | | | | | | |
| 1997 | 64 | 145 | 95 | 118 | 45 | 28 | **495** | |
| 1998 | 63 | 170 | 82 | 107 | 44 | 35 | **501** | |
| 1999 | 72 | 166 | 69 | 118 | 57 | 42 | **524** | |
| 2000 | 79 | 154 | 84 | 104 | 58 | 42 | **521** | |
| 2001 | 88 | 211 | 93 | 224 | 87 | 63 | **766** | |
| 2002 | 82 | 173 | 93 | 166 | 91 | 56 | **661** | |
| 2003 | 62 | 110 | 44 | 64 | 60 | 46 | **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** | |
| 2014 | 9 | 16 | 10 | 14 | 10 | 22 | **81** | |

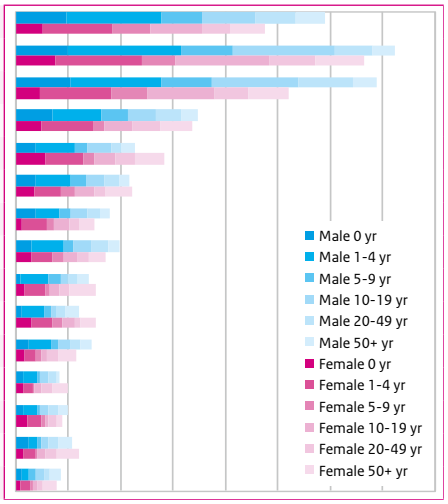



* Preliminary figures. Starting with statistical year 2013, the coding of causes of death is partly automatic.

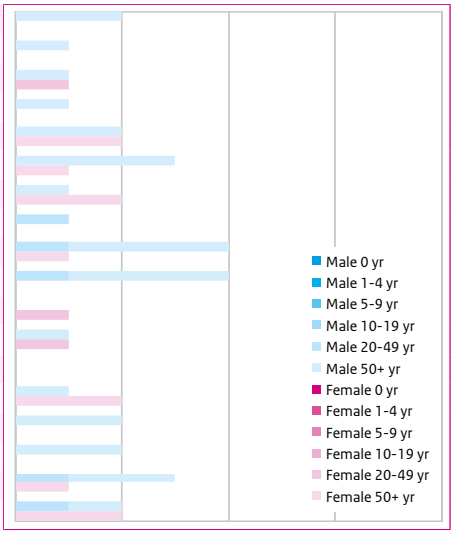
| Meningococcal disease | | | | | | | | ICD9: 036.0-4, 036.8-9<br>ICD10: A39 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Hospitalisations (036.0, 036.2-3)** | | | | | | | | |
| 1999 | 112 | 249 | 97 | 167 | 62 | 51 | **741** | |
| 2000 | 96 | 232 | 108 | 128 | 61 | 48 | **676** | |
| 2001 | 109 | 288 | 106 | 259 | 77 | 59 | **906** | |
| 2002 | 103 | 232 | 107 | 172 | 64 | 41 | **731** | |
| 2003 | 70 | 133 | 43 | 61 | 56 | 41 | **407** | |
| 2004 | 52 | 98 | 46 | 53 | 28 | 41 | **319** | |
| 2005 | 44 | 67 | 35 | 45 | 17 | 24 | **234** | |
| 2006 | 31 | 48 | 25 | 40 | 18 | 19 | **183** | |
| 2007 | 22 | 55 | 17 | 22 | 23 | 15 | **154** | |
| 2008 | 18 | 46 | 15 | 13 | 10 | 28 | **130** | |
| 2009 | 27 | 47 | 24 | 24 | 14 | 12 | **149** | |
| 2010 | 20 | 37 | 12 | 18 | 11 | 18 | **117** | |
| 2011 | 18 | 26 | 10 | 20 | 13 | 9 | **98** | |
| 2012 | 15 | 25 | 11 | 10 | 8 | 10 | **79** | |
| 2013 | 15 | 20 | 4 | 11 | 15 | 20 | **86** | |
| 2014** | 10 | 10 | 12 | 11 | 8 | 12 | **63** | |
| *Isolates**** | | | | | | | | |
| 2000 | 79 | 161 | 73 | 102 | 67 | 62 | **544** | |
| 2001 | 91 | 197 | 82 | 194 | 86 | 69 | **719** | |
| 2002 | 80 | 154 | 84 | 148 | 86 | 62 | **614** | |
| 2003 | 61 | 97 | 37 | 53 | 55 | 45 | **348** | |
| 2004 | 48 | 74 | 24 | 43 | 29 | 41 | **259** | |
| 2005 | 37 | 60 | 28 | 40 | 25 | 34 | **224** | |
| 2006 | 25 | 48 | 20 | 29 | 22 | 24 | **168** | |
| 2007 | 30 | 51 | 20 | 30 | 27 | 28 | **186** | |
| 2008 | 15 | 47 | 17 | 17 | 18 | 37 | **151** | |
| 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 | 36 | **115** | |
| 2014 | 10 | 16 | 10 | 12 | 11 | 23 | **82** | |

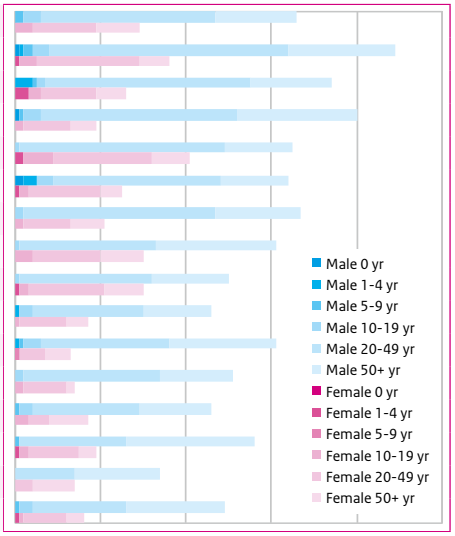



* Up to 2012, diseases are coded according to the ICD-9 coding system. Starting with 2013, diseases are coded according to the ICD-10 coding system.
* For 39 patients, the age is unknown.
** Preliminary and incomplete figures.
*** Nontypeables excluded.

| Hepatitis B | | | | | | | | ICD9: 070.2-3<br>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** | |
| 2013* | 0 | 0 | 0 | 0 | 1 | 3 | **4** | |
| 2014* | 0 | 0 | 0 | 0 | 1 | 3 | **4** | |
| *Hospitalisations*** | | | | | | | | |
| 1999 | 0 | 0 | 2 | 8 | 56 | 29 | **95** | |
| 2000 | 1 | 2 | 2 | 8 | 80 | 32 | **127** | |
| 2001 | 0 | 7 | 1 | 5 | 61 | 26 | **104** | |
| 2002 | 1 | 0 | 1 | 6 | 57 | 34 | **102** | |
| 2003 | 0 | 2 | 0 | 8 | 71 | 25 | **106** | |
| 2004 | 2 | 4 | 0 | 6 | 56 | 21 | **92** | |
| 2005 | 0 | 0 | 0 | 4 | 56 | 28 | **89** | |
| 2006 | 0 | 0 | 0 | 5 | 48 | 38 | **92** | |
| 2007 | 0 | 1 | 0 | 3 | 49 | 27 | **81** | |
| 2008 | 0 | 1 | 0 | 4 | 37 | 21 | **63** | |
| 2009 | 0 | 1 | 2 | 4 | 36 | 31 | **74** | |
| 2010 | 0 | 0 | 0 | 4 | 42 | 19 | **66** | |
| 2011 | 0 | 0 | 1 | 6 | 30 | 26 | **63** | |
| 2012 | 0 | 1 | 1 | 2 | 37 | 34 | **76** | |
| 2013 | 0 | 0 | 0 | 0 | 18 | 30 | **48** | |
| 2014*** | 0 | 1 | 1 | 4 | 32 | 27 | **66** | |



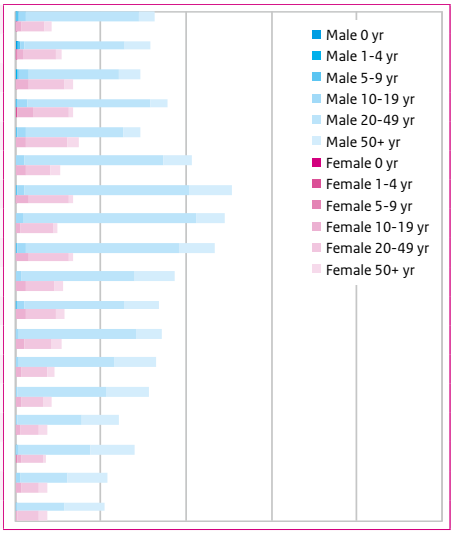

* Preliminary figures. Starting with statistical year 2013, the coding of causes of death is partly automatic.

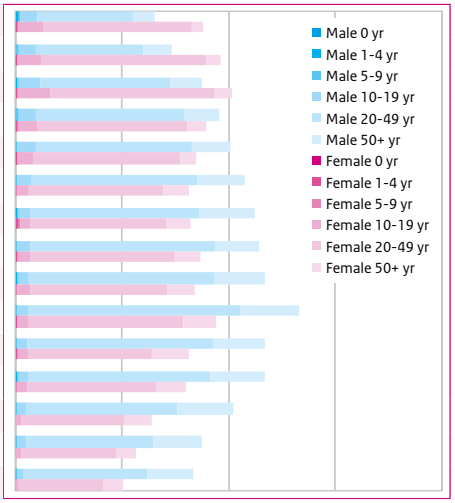
** Up to 2012, diseases are coded according to the ICD-9 coding system. Starting with 2013, diseases are coded according to the ICD-10 coding system.

** For 18 patients, the age is unknown.

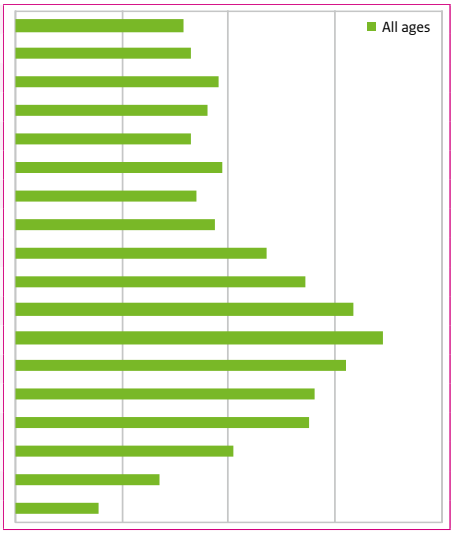
*** Preliminary and incomplete figures.

| Hepatitis B | | | | | | | | ICD9: 070.2-3<br>ICD10: B16, B17.0, B18.0, B18.1 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Notifications (Acute)* | | | | | | | | |
| 1997 | 1 | 1 | 3 | 15 | 158 | 28 | **206** | |
| 1998 | 3 | 1 | 5 | 10 | 157 | 37 | **213** | |
| 1999 | 0 | 4 | 1 | 26 | 148 | 35 | **214** | |
| 2000 | 0 | 3 | 1 | 31 | 186 | 26 | **247** | |
| 2001 | 0 | 0 | 2 | 23 | 163 | 33 | **221** | |
| 2002 | 0 | 0 | 0 | 22 | 193 | 44 | **259** | |
| 2003 | 0 | 1 | 3 | 22 | 240 | 56 | **322** | |
| 2004 | 0 | 1 | 0 | 15 | 240 | 40 | **296** | |
| 2005 | 0 | 0 | 2 | 26 | 227 | 46 | **301** | |
| 2006 | 0 | 0 | 0 | 20 | 166 | 56 | **242** | |
| 2007 | 0 | 1 | 1 | 20 | 154 | 50 | **226** | |
| 2008 | 0 | 0 | 1 | 13 | 170 | 41 | **225** | |
| 2009 | 0 | 0 | 0 | 11 | 144 | 56 | **211** | |
| 2010 | 0 | 0 | 0 | 10 | 129 | 60 | **199** | |
| 2011 | 0 | 0 | 1 | 7 | 98 | 53 | **159** | |
| 2012 | 0 | 1 | 2 | 9 | 108 | 54 | **174** | |
| 2013 | 0 | 0 | 0 | 12 | 77 | 56 | **145** | |
| 2014 | 0 | 0 | 1 | 3 | 81 | 56 | **141** | |
| *Notifications (Chronic)* | | | | | | | | |
| 2000 | 2 | 16 | 15 | 149 | 919 | 121 | **1,222** | |
| 2001 | 2 | 7 | 12 | 158 | 1,018 | 159 | **1,356** | |
| 2002 | 0 | 11 | 15 | 200 | 1,099 | 183 | **1,508** | |
| 2003 | 3 | 7 | 15 | 132 | 1,126 | 197 | **1,480** | |
| 2004 | 2 | 5 | 8 | 128 | 1,139 | 208 | **1,490** | |
| 2005 | 0 | 3 | 9 | 97 | 1,134 | 268 | **1,511** | |
| 2006 | 2 | 18 | 8 | 85 | 1,141 | 300 | **1,554** | |
| 2007 | 0 | 8 | 9 | 95 | 1,233 | 265 | **1,610** | |
| 2008 | 0 | 10 | 6 | 87 | 1,215 | 295 | **1,613** | |
| 2009 | 0 | 7 | 7 | 85 | 1,373 | 348 | **1,820** | |
| 2010 | 0 | 9 | 12 | 77 | 1,159 | 328 | **1,585** | |
| 2011 | 0 | 9 | 10 | 77 | 1,162 | 319 | **1,577** | |
| 2012 | 0 | 3 | 3 | 55 | 959 | 307 | **1,327** | |
| 2013 | 0 | 4 | 5 | 54 | 829 | 261 | **1,153** | |
| 2014 | 1 | 5 | 3 | 31 | 787 | 247 | **1,074** | |

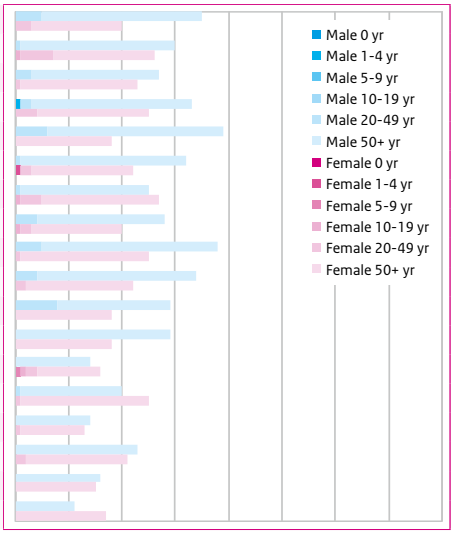


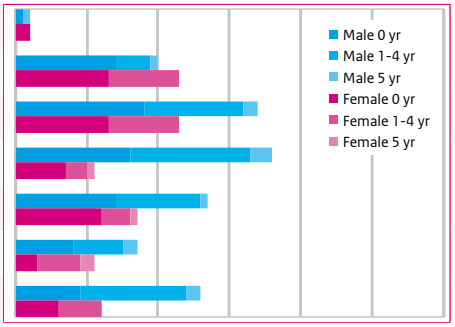



| Hepatitis B | | | | | | | | ICD9: 070.2-3<br>ICD10: B16, B17.0, B18.0, B18.1 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Laboratory diagnoses* | | | | | | | | |
| 1997 | - | - | - | - | - | - | **787** | |
| 1998 | - | - | - | - | - | - | **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** | |
| 2014 | - | - | - | - | - | - | **392** | |



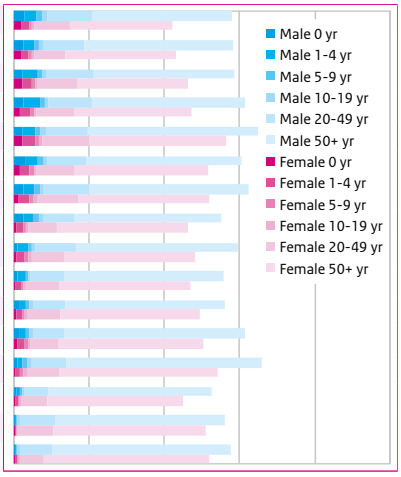
| Pneumococcal disease | | | | | | | | ICD9: 0382, 481, 4823, 3201<br>ICD10: J13, 18.0, 18.9, G00.1, A40.4 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Mortality (J13; Pneumonia)* | | | | | | | | |
| 1997 | 0 | 0 | 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** | |
| 2013* | 0 | 0 | 0 | 0 | 0 | 31 | **31** | |
| 2014* | 0 | 0 | 0 | 0 | 0 | 28 | **28** | |
| *Notifications*** | | | | | | | | |
| 2008 | 3 | 0 | 1** | - | - | - | **4** | |
| 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** | |
| 2014 | 15 | 21 | 2** | - | - | - | **38** | |

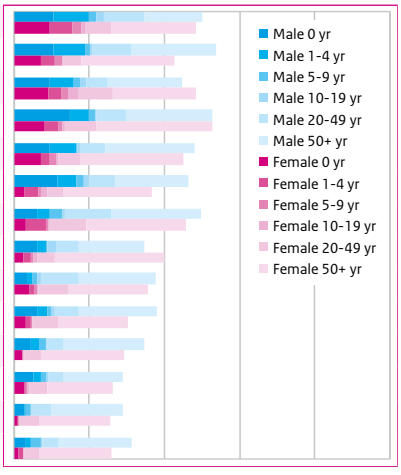



* Preliminary figures. Starting with statistical year 2013, the coding of causes of death is partly automatic.
** Notifiable for 0 to 5 year-old children.

| Pneumococcal disease | | | | | | | | ICD9: 0382, 481, 4823, 3201<br>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+ | | |
| *Hospitalisations** | | | | | | | | |
| 1999 | 123 | 125 | 63 | 51 | 527 | 1,619 | **2,513** | |
| 2000 | 112 | 110 | 60 | 53 | 475 | 1,725 | **2,540** | |
| 2001 | 107 | 169 | 52 | 47 | 575 | 1,671 | **2,628** | |
| 2002 | 96 | 185 | 61 | 42 | 543 | 1,789 | **2,722** | |
| 2003 | 108 | 171 | 56 | 71 | 586 | 2,034 | **3,042** | |
| 2004 | 119 | 143 | 64 | 43 | 518 | 1,918 | **2,810** | |
| 2005 | 92 | 144 | 67 | 49 | 574 | 1,932 | **2,867** | |
| 2006 | 76 | 115 | 56 | 44 | 397 | 1,853 | **2,545** | |
| 2007 | 42 | 122 | 53 | 45 | 483 | 1,945 | **2,699** | |
| 2008 | 33 | 90 | 34 | 31 | 449 | 1,932 | **2,575** | |
| 2009 | 53 | 77 | 38 | 47 | 430 | 1,991 | **2,643** | |
| 2010 | 63 | 83 | 48 | 41 | 385 | 2,180 | **2,807** | |
| 2011 | 36 | 57 | 62 | 50 | 446 | 2,348 | **3,001** | |
| 2012 | 24 | 43 | 18 | 29 | 338 | 1,983 | **2,438** | |
| 2013 | 15 | 11 | 13 | 23 | 474 | 2,140 | **2,678** | |
| 2014** | 21 | 15 | 17 | 26 | 369 | 2,291 | **2,742** | |
| *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** | |
| 2014 | 11 | 6 | 7 | 2 | 21 | 96 | **143** | |



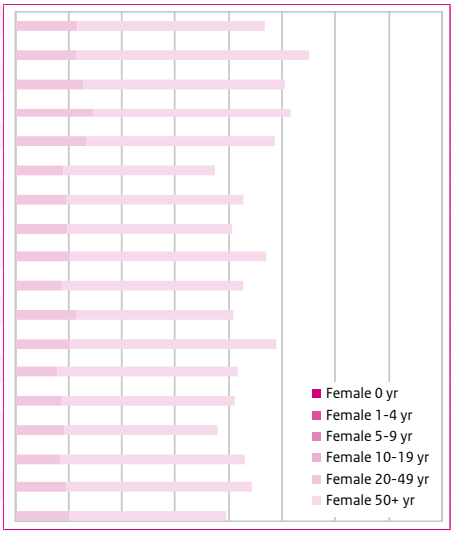



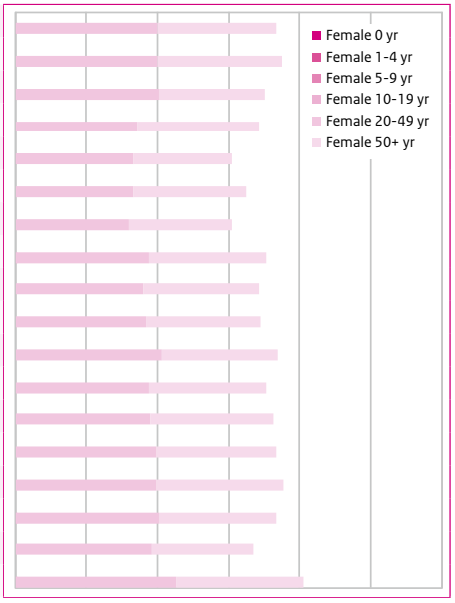

* Up to 2012, diseases are coded according to the ICD-9 coding system. Starting with 2013, diseases are coded according to the ICD-10 coding system.

* For 96 patients, the age is unknown.

** Preliminary and incomplete figures.

| 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** | |
| 2013* | 0 | 0 | 0 | 0 | 47 | 175 | **222** | |
| 2014* | 0 | 0 | 0 | 0 | 50 | 148 | **198** | |
| *Registrations (Cervical Cancer)*** | | | | | | | | |
| 1997 | 0 | 0 | 0 | 2 | 397 | 336 | **735** | |
| 1998 | 0 | 0 | 0 | 0 | 398 | 353 | **751** | |
| 1999 | 0 | 0 | 0 | 1 | 401 | 300 | **702** | |
| 2000 | 0 | 0 | 0 | 0 | 345 | 341 | **686** | |
| 2001 | 0 | 0 | 0 | 1 | 331 | 275 | **607** | |
| 2002 | 0 | 0 | 0 | 0 | 333 | 318 | **651** | |
| 2003 | 0 | 0 | 0 | 0 | 318 | 291 | **609** | |
| 2004 | 0 | 0 | 0 | 1 | 374 | 331 | **706** | |
| 2005 | 0 | 0 | 0 | 0 | 358 | 326 | **684** | |
| 2006 | 0 | 0 | 0 | 0 | 367 | 322 | **689** | |
| 2007 | 0 | 0 | 0 | 0 | 411 | 328 | **739** | |
| 2008 | 0 | 0 | 0 | 0 | 375 | 332 | **707** | |
| 2009 | 0 | 0 | 0 | 0 | 381 | 343 | **724** | |
| 2010 | 0 | 0 | 0 | 0 | 396 | 339 | **735** | |
| 2011 | 0 | 0 | 0 | 0 | 394 | 359 | **753** | |
| 2012 | 0 | 0 | 0 | 2 | 402 | 331 | **736** | |
| 2013 | 0 | 0 | 0 | 0 | 384 | 284 | **668** | |
| 2014*** | 0 | 0 | 0 | 1 | 452 | 359 | **812** | |



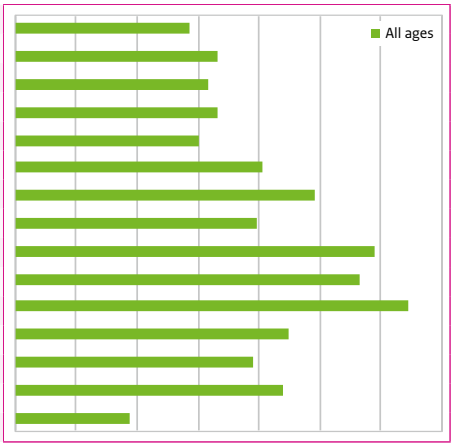



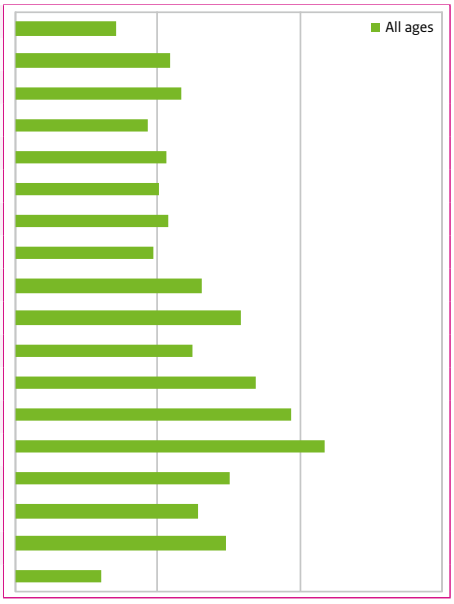

* Preliminary figures. Starting with statistical year 2013, the coding of causes of death is partly automatic.
** Source: Netherlands Cancer Registry (NKR).
*** Preliminary figures.

## Rotavirus

| Year | Age (years) | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | 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 | - | - | - | - | - | - | **3,892** |
| 2013 | - | - | - | - | - | - | **4,399** |
| 2014** | - | - | - | - | - | - | **1,865** |
| *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 | - | - | - | - | - | - | **1,505** |
| 2012 | - | - | - | - | - | - | **1,287** |
| 2013 | - | - | - | - | - | - | **1,487** |
| 2014 | - | - | - | - | - | - | **607** |

**N**

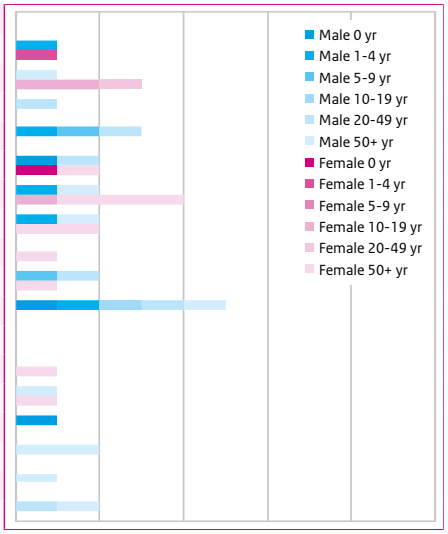


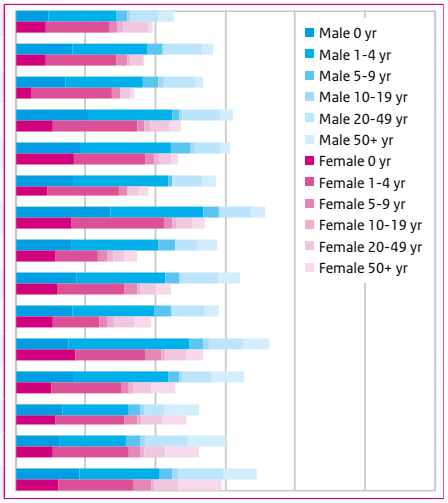




* Up to 2012, diseases are coded according to the ICD-9 coding system. Starting with 2013, diseases are coded according to the ICD-10 coding system.

** Preliminary and incomplete figures.

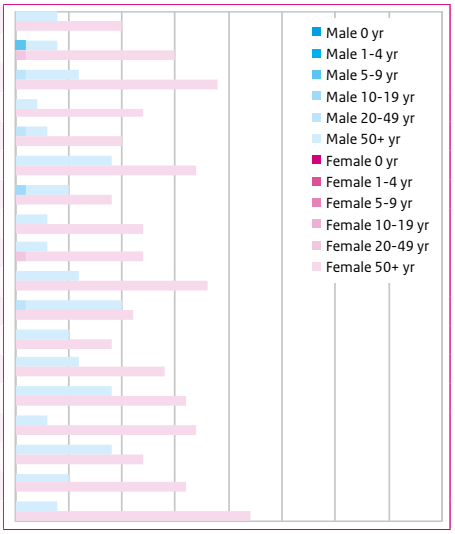
| Varicella (Chickenpox) | | | | | | | | ICD9: 052<br>ICD10: B01 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Mortality* | | | | | | | | |
| 1997 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 1998 | 0 | 2 | 0 | 0 | 0 | 0 | **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** | |
| 2013* | 0 | 0 | 0 | 0 | 0 | 1 | **1** | |
| 2014* | 0 | 0 | 0 | 0 | 1 | 1 | **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** | |
| 2013 | 58 | 102 | 18 | 7 | 45 | 51 | **281** | |
| 2014*** | 77 | 110 | 22 | 6 | 49 | 55 | **319** | |

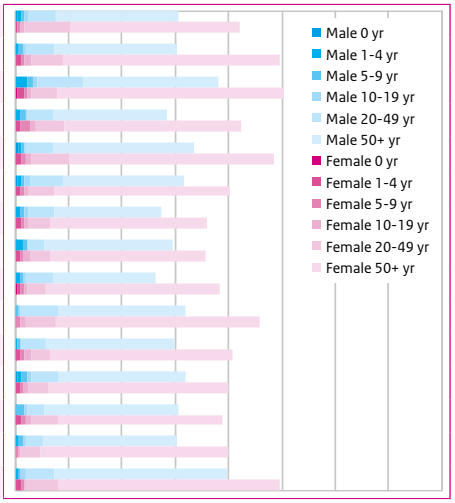



* Preliminary figures. Starting with statistical year 2013, the coding of causes of death is partly automatic.
** Up to 2012, diseases are coded according to the ICD-9 coding system. Starting with 2013, diseases are coded according to the ICD-10 coding system.
*** Preliminary and incomplete figures.

| Herpes zoster (Shingles) | | | | | | | | ICD9: 053<br>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** | |
| 2013* | 0 | 0 | 0 | 0 | 0 | 21 | **21** | |
| 2014* | 0 | 0 | 0 | 0 | 0 | 26 | **26** | |
| *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** | |
| 2013 | 1 | 3 | 6 | 5 | 34 | 302 | **351** | |
| 2014*** | 0 | 9 | 4 | 7 | 56 | 370 | **446** | |



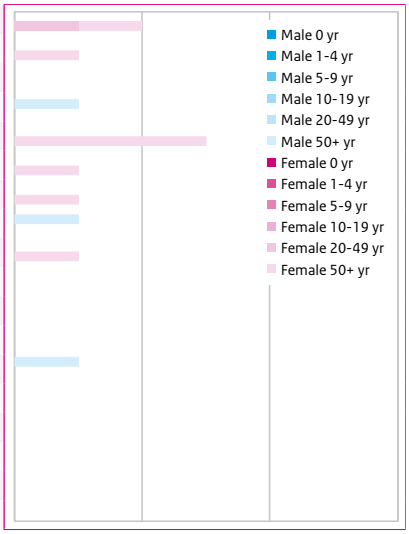



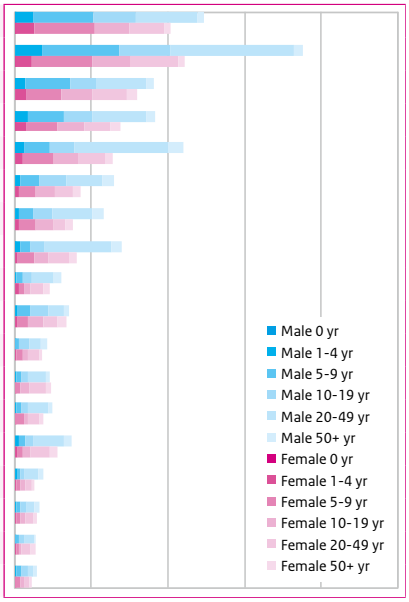

* Preliminary figures. Starting with statistical year 2013, the coding of causes of death is partly automatic.

** Up to 2012, diseases are coded according to the ICD-9 coding system. Starting with 2013, diseases are coded according to the ICD-10 coding system.

*** Preliminary and incomplete figures.

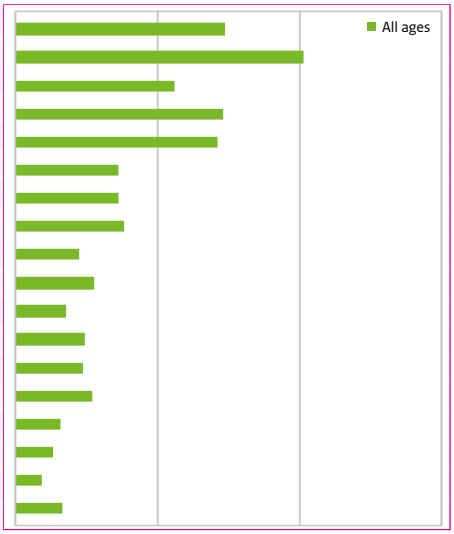
| Hepatitis A | | | | | | | | ICD10: B15 |
|---|---|---|---|---|---|---|---|---|
| Year | Age (years) | | | | | | Total | N |
| | 0 | 1-4 | 5-9 | 10-19 | 20-49 | 50+ | | |
| *Mortality (Acute)* | | | | | | | | |
| 1997 | 0 | 0 | 0 | 0 | 1 | 1 | **2** | |
| 1998 | 0 | 0 | 0 | 0 | 0 | 1 | **1** | |
| 1999 | 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** | |
| 2013* | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| 2014* | 0 | 0 | 0 | 0 | 0 | 0 | **0** | |
| *Notifications* | | | | | | | | |
| 1997 | 3 | 96 | 318 | 199 | 253 | 37 | **913**** | |
| 1998 | 1 | 114 | 360 | 235 | 446 | 47 | **1,210**** | |
| 1999 | 2 | 58 | 210 | 148 | 217 | 53 | **694**** | |
| 2000 | 3 | 63 | 174 | 146 | 205 | 54 | **647**** | |
| 2001 | 2 | 43 | 149 | 126 | 318 | 63 | **704**** | |
| 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 | 49 | 20 | **110** | |
| 2014 | 0 | 5 | 26 | 27 | 30 | 17 | **105** | |



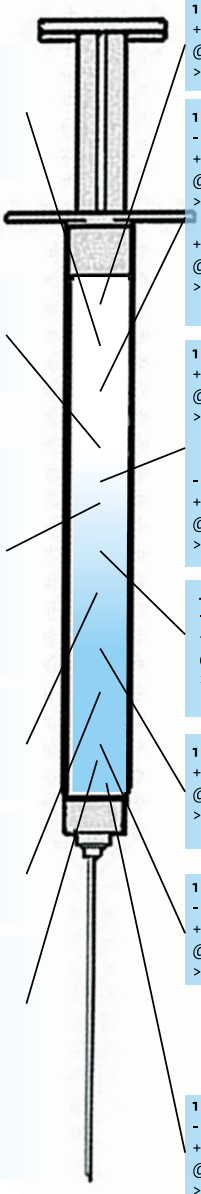




* Preliminary figures. Starting with statistical year 2013, the coding of causes of death is partly automatic.
** For 25 patients, the age is unknown.

| 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** | |
| 2014 | - | - | - | - | - | - | **66** | |



# Appendix 3 Overview of changes in the NIP since 2000



**1 September 2002**
+ NeisVac-C (Baxter)
@ 14 months of age
> Children born on or after 1 June 2001
# Catch-up campaign in June 2002 for birth cohorts 1 June 1983 to 31 May 2001

**1 January 2005**
- DTwP-IPV/Hib vaccine (NVI)
+ Infanrix IPV+Hib (GSK)
@ 2,3,4 and 11 months of age
> Children born on or after 1 February 2004

**1 June 2006**
+ Prevnar (Wyeth)
@ 2,3,4 and 11 months of age
> Children born on or after 1 April 2006

- Pediacel (SP MSD)
+ Infanrix hexa (GSK)
@ 2,3,4 and 11 months of age
> Children born on or after 1 April 2006
(specific risk groups [1]

**September/October 2006**
- MMR vaccine (NVI)
+ MMR-VaxPro (SP MSD) and Priorix (GSK)
@ 14 months of age
> Children born on or after July/August 2005

**1 February 2008**
- Triaxis Polio (SP MSD) [4]
+ Infanrix IPV (GSK)
@ 4 years of age
> Children born on or after 1 February 2004

**1 September 2008**
- HBVAXPRO (SP MSD)
+ Engerix-B Junior (GSK)
@ birth
> Children born on or after 1 September 2008
(specific risk groups [3])

- MMR vaccine (NVI)
+ Priorix (GSK)
@ 9 years of age
> Children born on or after 1 September 1999

**1 July 2001**
+ Acellular pertussis vaccine (GSK)
@ 4 years of age
> Children born on or after 1 January 1998

**1 March 2003**
- DTwP-IPV vaccine (NVI) and Hib vaccine (NVI)
+ DTwP-IPV/Hib vaccine (NVI)
@ 2,3,4 and 11 months of age
> Children born on or after 1 April 2002

+ HBVAXPRO (SP MSD)
@ 2,3,4 and 11 months of age
> Children born on or after 1 January 2003
(specific risk groups [1])

**1 January 2006**
+ HBVAXPRO (SP MSD)
@ birth
> Children born on or after 1 January 2006
(specific risk groups [2])

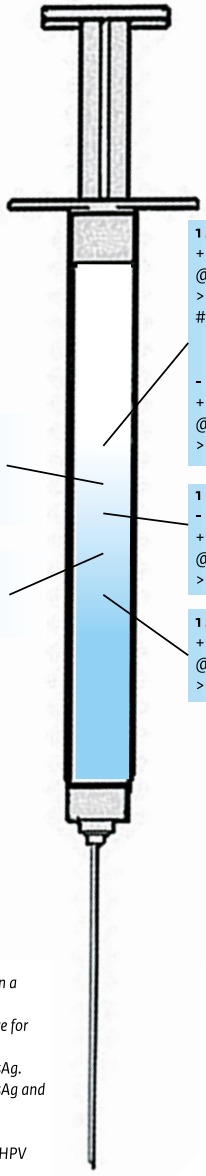
- Infanrix IPV+Hib (GSK)
+ Pediacel (SP MSD)
@ 2,3,4 and 11 months of age
> Children born on or after 1 February 2005

**July/August 2006**
- DT-IPV vaccine (NVI) and Acellular pertussis vaccine (GSK)
+ Triaxis Polio (SP MSD)
@ 4 years of age
> Children born on or after July/August 2002

**1 January 2008**
+ HBVAXPRO (SP MSD)
@ birth
> Children born on or after 1 January 2008
(specific risk groups [3]

**1 July-mid Decenber 2008**
- Pediacil (SP MSD)
+ Infanrix IPV+Hib (GSK)
@ 2,3,4 and 11 months of age
> Children born on or after 1 August 2007

**1 October 2008**
- Priorix (GSK)
+ MMR-VaxPro (SP MSD) and Priorix (GSK)
@ 9 years of age
> Children born on or after 1 October 1999



**1 January 2010**
+ Cervarix (GSK)
@ 12 years of age [5]
> Children born on or after 1 January 1997
# Catch-up campaign for birth cohorts 1 January 1993 to 31 December 1996

- Pediacel (SP MSD) and Infanrix IPV+Hib (GSK)
+ Pediacel (SP MSD)
@ 2,3,4 and 11 months of age
> Children born on or after 1 February 2009

**1 May 2011**
- Prevenar (Wyeth)
+ Synflorix (GSK)
@ 2,3,4 and 11 months of age
> Children born on or after 1 March 2011

**1 October 2011**
- Pediacel (SP MSD)
+ Infanrix hexa (GSK)
@ 2,3,4 and 11 months of age
> Children born on or after 1 August 2011

**1 December 2013**
+ Synflorix (GSK)
@ 2,4 and 11 months of age
> Children born on or after 1 October 2013

**1 January 2014**
+ Cervarix (GSK)
@ 12 years [6]
> Children born on or after 1 January 2001

*[1] 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.*
*[2] Only for children whose mother tested positive for HBsAg.*
*[3] Only for children whose mother tested positive for HBsAg and children with Down syndrome.*
*[4] Used until March 2008.*
*[5] Only girls were vaccinated and received three doses of HPV vaccine: at 0, 1 and 6 months.*
*[6] Only girls were vaccinated and received two doses of HPV vaccine: at 0 and 6 months.*

***Legend***
- *old vaccine (manufacturer)*
+ *new vaccine (manufacturer)*
@ *age*
> *the birth cohort from which children received at least one injection of the newly introduced vaccination*
\# *additional information*

## Appendix 4 Composition of currently used vaccines in the NIP

| Vaccine | Composition |
|---|---|
| **M-M-R VaxPro / SP MSD**<br>EU/1/06/337<br>Mumps, measles and rubella vaccine<br>0.5 ml | Mumps virus (Jeryl Lynn) > 12,500 TCID50<br>(tissue culture infectious doses)<br>Measles virus (Enders' Edmonston) > 1000 TCID50<br>Rubella virus (Wistar RA 27/3) > 1000 TCID50 |
| **Infanrix IPV / GSK**<br>RVG 34568<br>Diphtheria, tetanus, pertussis (acellular component), inactivated poliomyelitis vaccine<br>0.5 ml | Adsorbed diphtheria toxoid > 30 IU<br>Adsorbed tetanus toxoid > 40 IU<br>Adsorbed pertussis toxoid (PT) 25 µg<br>Adsorbed filamentous haemagglutinin (FHA) 25 µg<br>Absorbed pertactin (PRN) 8 µg<br>Inactivated type 1 poliovirus (Mahoney) 40 DU<br>Inactivated type 2 poliovirus (MEF-1) 8 DU<br>Inactivated type 3 poliovirus (Saukett) 32 DU |
| **Infanrix Hexa/GSK**<br>EU/1/00/152<br>Diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), inactivated poliomyelitis vaccine and conjugated *Haemophilus influenzae* type b-vaccine (adsorbed)<br>0.5 ml | Adsorbed diphtheria toxoid > 30 IU<br>Adsorbed tetanus toxoid > 40 IU<br>Adsorbed pertussis toxoid (PT) 25 µg<br>Adsorbed filamentous haemagglutinin (FHA) 25 µg<br>Adsorbed pertactin (PRN) 8 µg<br>Adsorbed recombinant HBsAg protein 10 µg<br>Inactivated type 1 poliovirus (Mahoney) 40 DU<br>Inactivated type 2 poliovirus (MEF-1) 8 DU<br>Inactivated type 3 poliovirus (Saukett) 32 DU<br>Adsorbed purified capsular polysaccharide of Hib (PRP) 10 µg covalently bound to tetanus toxoid (T) 20-40 µg |
| **DT-IPV vaccine/NVI**<br>RVG 17641<br>Diphtheria (adsorbed), tetanus (adsorbed) and inactivated poliomyelitis vaccine<br>1 ml | Diphtheria-toxoid* > 5 IU<br>Tetanus toxoid* > 20 IU<br>Inactivated poliovirus type 1 > 40 DU<br>Inactivated poliovirus type 2 > 4 DU<br>Inactivated poliovirus type 3 > 7.5 DU<br>*adsorbed to aluminium phosphate 1.5 mg $Al^{3}$+ |

| Vaccine | Composition |
|---|---|
| **Engerix-B Junior**<br>RVG24290<br>Hepatitis B vaccine (recombinant)<br>0.5 ml | Hepatitis B-virus surface antigen, recombinant*<br>(S protein) absorbed 10 µg<br>*produced on genetically-engineered yeast cells (Saccharomyces cerevisiae) |
| **HBVAXPRO**<br>RVG17316<br>Hepatitis B vaccine (rDNA)<br>0.5 ml | Hepatitis B virus surface antigen, recombinant (HBsAg)[1,2] 5 µg<br>[1] Adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.25 mg Al+)<br>[2] Produced in Saccharomyces cerevisiae (strain [2]150-2-3) yeast by recombinant DNA technology |
| **Act-HIB**<br>*Haemophilus influenzae* type b Conjugate Vaccine (Tetanus Protein - Conjugate)<br>0.5 ml | Purified polyribose ribitol phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b[1] 10 µg<br>[1]covalently bound to tetanus protein 20 µg |
| **Cervarix / GSK**<br>EU/1/07/419 | Human papillomavirus type 16 L1 protein[2,3,4] 20 µg<br>Human papillomavirus type 18 L1 protein[2,3,4] 20 µg<br>[1] adjuvanted by AS04 containing 3-O-desacyl-4'-monophosphoryl lipid A (MPL)[3] 50 µg<br>[2] absorbed on aluminium hydroxide, hydrated ($Al(OH)^3$) 0.5 mg $AL^{3+}$ in total<br>[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*. |
| **NeisVac-C/Baxter**<br>RVG 26343<br>Conjugated meningococcal C saccharide vaccine (adsorbed)<br>0.5 ml | Neisseria meningitidis (C11-strain)<br>Polysaccharide O-deacetylated 10 µg<br>conjugated to tetanus toxoid 10-20 µg<br>adsorbed to aluminium hydroxide 0.5 mg $Al^{3+}$ |

| Vaccine | Composition |
|---|---|
| **Synflorix/GSK**<br>EU/1/09/508<br>Pneumococcal polysaccharide conjugate vaccine (adsorbed)<br>0.5 ml | Pneumococcal polysaccharide serotype 1[1,2] 1 µg<br>Pneumococcal polysaccharide serotype 4[1,2] 3 µg<br>Pneumococcal polysaccharide serotype 5[1,2] 1 µg<br>Pneumococcal polysaccharide serotype 6B[1,2] 1 µg<br>Pneumococcal polysaccharide serotype 7F[1,2] 1 µg<br>Pneumococcal polysaccharide serotype 9V[1,2] 1 µg<br>Pneumococcal polysaccharide serotype 14[1,2] 1 µg<br>Pneumococcal polysaccharide serotype 18C[1,3] 3 µg<br>Pneumococcal polysaccharide serotype 19F[1,4] 3 µg<br>Pneumococcal polysaccharide serotype 23F[1,2] 1 µg<br>[1] absorbed to aluminium phosphate 0.5 mg $Al^{3+}$<br>[2] conjugated to protein D (obtained from nontypeable *Haemophilus influenzae*) carrier protein 9-16 mg<br>[3] conjugated to tetanus toxoid 5-10 mg<br>[3] conjugated to diphtheria toxoid 3-6 mg |

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

# Appendix 5 Overview of relevant websites

**General information for NIP professionals**
RIVM website for professionals:
*http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/ Professionals*

Dienst Vaccinvoorziening en Preventieprogramma's (DVP):
*http://www.rivm.nl/RIVM/Organisatie/Centra/Dienst_Vaccinvoorziening_en_Preventieprogramma_s*

Training:
*http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/ Professionals/Scholingsbijeenkomsten*

Meldingsplicht infectieziekten:
*http://www.rivm.nl/Onderwerpen/M/Meldingsplicht_infectieziekten*

**General information for the public**
RIVM websites for the public:
*http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma*

*www.rijksvaccinatieprogramma.nl*

Volksgezondheidenzorg.info:
*https://www.volksgezondheidenzorg.info/*

Cervical cancer screening programme:
*http://www.rivm.nl/Onderwerpen/B/Bevolkingsonderzoek_ baarmoederhalskanker*

**Other NIP-related RIVM reports**
Vaccinatiegraad Rijksvaccinatieprogramma Nederland, Verslagjaar 2015:
*http://www.rivm.nl/bibliotheek/rapporten/2015-0067.pdf*

Terugblik Rijksvaccinatieprogramma 2014:
*http://www.rivm.nl/bibliotheek/rapporten/2015-0089.pdf*

Adverse Events in the Netherlands Vaccination Programme, Reports in 2010 and Review 1994-2010: *http://www.rivm.nl/bibliotheek/rapporten/205051004.pdf*

## Product information

M-M-RVAXPRO (MMR):
*http://www.rivm.nl/dsresource?objectid=rivmp:183945&type=org& disposition=inline*

Infanrix-IPV (DKTP):
*http://www.rivm.nl/dsresource?objectid=rivmp:60726&type=org& disposition=inline*

Infanrix Hexa (DKTP-Hib-HepB):
*http://www.rivm.nl/dsresource?objectid=rivmp:116776&type=org& disposition=inline*

DTP (DTP):
*http://www.rivm.nl/dsresource?objectid=rivmp:119441&type=org& disposition=inline*

Engerix-B Junior (HepB):
*http://www.rivm.nl/dsresource?objectid=rivmp:60837&type=org& disposition=inline*

HBVAXPRO (HepB adults):
*http://www.rivm.nl/dsresource?objectid=rivmp:60857&type=org& disposition=inline*

Act-HIB (Hib):
*http://www.rivm.nl/dsresource?objectid=rivmp:60910&type=org& disposition=inline*

Cervarix (HPV):
*http://www.rivm.nl/dsresource?objectid=rivmp:116768&type=org& disposition=inline*

NeisVac-C (MenC):
*http://www.rivm.nl/dsresource?objectid=rivmp:60983&type=org& disposition=inline*

Synflorix (Pneumokokken):
*http://www.rivm.nl/dsresource?objectid=rivmp:116782&type=org& disposition=inline*

## National organisations

Ministry of Health, Welfare and Sports:
*http://www.rijksoverheid.nl/onderwerpen/vaccinaties*

Health Council:
*http://www.gezondheidsraad.nl/*

GGD GHOR:
*http://www.ggdghorkennisnet.nl/*

### *Safety of vaccines*

Netherlands Pharmacovigilance Centre Lareb:
*http://www.lareb.nl/*

College ter Beoordeling van Geneesmiddelen (CBG):
*http://www.cbg-meb.nl/*

*Data sources*
Statistics Netherlands (CBS):
*http://www.cbs.nl/*

Dutch Hospital Data (DHD):
*https://www.dhd.nl/*

Nederlands instituut voor onderzoek van de gezondheidszorg (NIVEL):
*http://www.nivel.nl/*

Nederlands Referentielaboratorium voor Bacteriële Meningitis (NRBM):
*https://www.amc.nl/web/Het-AMC/Afdelingen/Medische-afdelingen/Medische-Microbiologie/Onderafdelingen/Het-Nederlands-Referentielaboratorium-voor-Bacteriele-Meningitis.htm*

Integrated Primary Care Information (IPCI):
*http://www.ipci.nl/*

*Other research partners*
TNO:
*https://www.tno.nl/*

Nederlandse Werkgroep Klinische Virologie (NWKV):
*http://www.nvmm.nl/nwkv*

**International organisations**
World Health Organization (WHO):
*http://www.who.int/en/*

World Health Organization (WHO) Europe:
*http://www.euro.who.int/en/home*

European Centre for Disease Prevention and Control (ECDC):
*http://ecdc.europa.eu/en/*

Centers for Disease Control and Prevention (CDC):
*http://www.cdc.gov/*

ClinicalTrials.gov:
*https://clinicaltrials.gov/*

*Advisory Committees*

Joint Committee on Vaccination and Immunisation (JCVI):
*https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation*

Advisory Committee on Immunization Practices (ACIP):
*http://www.cdc.gov/vaccines/acip/*

Standing Committee on Vaccination (STIKO):
*http://www.rki.de/EN/Content/Prevention/Vaccination/Vaccination_node.html*

*Safety of vaccines*

European Medicines Agency (EMA):
*http://www.ema.europa.eu/ema/*

U.S. Food and Drug Administration (FDA):
*http://www.fda.gov/*

*International networks*

EUVAC-Net:
*http://ecdc.europa.eu/en/healthtopics/vaccine-preventable-diseases/euvac/Pages/index.aspx*

Vaccine European New Integrated Collaboration Effort (VENICE) III project:
*http://venice.cineca.org/*

HAVNET:
*http://www.rivm.nl/en/Topics/H/HAVNET*

National Immunization Technical Advisory Groups (NITAGs):
*http://www.nitag-resource.org/*

*Communication platforms*

Epidemic Intelligence Information System (EPIS):
*http://ecdc.europa.eu/en/activities/epidemicintelligence/Pages/EpidemicIntelligence_Tools.aspx*

## Vaccination of risk groups

*Influenza vaccination*

RIVM website on Influenza vaccination:
*http://www.rivm.nl/Onderwerpen/G/Griep/Griepprik*

*Stichting Nationaal Programma Grieppreventie (SNPG):*
*http://www.snpg.nl/*

Scientific Institute for Quality of Healthcare:
*http://www.iqhealthcare.nl/nl/*

Jaarrapportage Surveillance Respiratoire Infectieziekten 2013:
*http://www.rivm.nl/bibliotheek/rapporten/150002006.pdf*

*Tuberculosis*

KNCV Tuberculosis foundation:
*http://www.kncvtbc.nl/*

Jaarrapportage Surveillance Respiratoire Infectieziekten 2013:
*http://www.rivm.nl/bibliotheek/rapporten/150002006.pdf*

Nationaal plan tuberculosebestrijding 2011-2015:
*http://www.rivm.nl/bibliotheek/rapporten/215081001.pdf*

*Travellers vaccination*

Landelijk Coördinatiecentrum Reizigersadvisering:
*http://www.lcr.nl/Vaccinaties*

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