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 2017-2018

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Contents

Synopsis

The National Immunisation Programme in the Netherlands

Surveillance and developments in 2017-2018

In 2017, about 760,000 children aged 0 to 19 years received a total of 2,140,000 vaccinations within the National Immunisation Programme (NIP). Participation in the NIP was high among children under 10 years of age, despite the drop by around 2-3% for most vaccinations since 2014. An exception in the high participation is the number of girls who was vaccinated against human papillomavirus (HPV), which has declined by 15% since 2016. The number of reports (1,383) of possible adverse events following immunisation in 2017 was lower than the number of reports in 2016 (1,483).

NIP target diseases

There is an ongoing increase in the number of cases with meningococcal serogroup W (MenW) disease with 80 cases reported in 2017 and 78 up to August 2018. Because of this increase, since May 2018, the MenC vaccination given at 14 months of age has been replaced by a quadrivalent MenACWY vaccination. The case fatality of MenW disease (17%) was substantially higher than for other serogroups.

In 2017, the number of measles cases was low (16 reported cases) but higher than in the previous two years. The number of pertussis reports in 2017 was comparable with 2016 (28.7 compared with 32.6 per 10,000). Three people died from pertussis, one infant and two elderly. The number of reports of acute hepatitis B infections stayed stable (0.7 per 100,000 population). Also, the incidence of vaccine type invasive pneumococcal disease (IPD) remained very low in 2017/2018. Once again, the number of reported cases were in 2017 low for mumps (46), *Haemophilus influenzae* type b (Hib; 46), meningococcal serogroep C (MenC; 9), diphtheria (4), tetanus (1), rubella (0) and polio (0).

The inhabitants of Bonaire, St. Eustatius and Saba are predominantly well protected against NIP diseases. However, protection against measles and diphtheria is suboptimal for some age groups. Awareness is needed to prevent these diseases from spreading from neighboring countries, where outbreaks currently are observed.

New advice and decisions

In July 2018, the Ministry of Health, Welfare and Sports decided to expand the MenACWY vaccination outbreak programme to 13-14 year olds. In 2019, there will be a catch up campaign for all 15-18 year olds. Furthermore, it was decided that vaccination against disease caused by rotavirus will be included in the NIP for risk groups, and that maternal pertussis vaccination in the NIP will be organised by youth health care organisations.
The Dutch Health Council advises to offer vaccination against pneumococcal disease to the people 60 years and older.

Keywords: National Immunisation Programme (NIP), diphtheria, *Haemophilus influenzae*, hepatitis B, human papillomavirus (HPV), measles, meningococcal disease, mumps, pertussis, pneumococcal disease, poliomyelitis, rubella, tetanus, hepatitis A, respiratory syncytial virus (RSV), rotavirus, varicella zoster virus (VZV)

Publiekssamenvatting

Het Rijksvaccinatieprogramma in Nederland

Surveillance en ontwikkelingen in 2017-2018

In 2017 kregen ongeveer 760.000 kinderen van 0 tot 19 jaar samen 2.140.000 vaccinaties vanuit het Rijksvaccinatieprogramma (RVP). De deelname aan het RVP is hoog onder kinderen jonger dan 10 jaar, ondanks de daling van ongeveer 2 tot 3 procent voor de meeste vaccinaties sinds 2014. Een uitzondering op de hoge deelname is het aantal meisjes dat zich tegen het humaan papillomavirus (HPV) heeft laten vaccineren, dat met 15 procent is gedaald sinds 2016. Het aantal meldingen (1383) van mogelijke bijwerkingen van vaccins in 2017 was lager dan het jaar ervoor (1483).

RVP-ziekten

Het aantal patiënten met meningokokkenziekte door MenW blijft stijgen, met 80 patiënten in 2017 en 78 tot en met augustus 2018. Daarom is sinds mei 2018 de MenC-vaccinatie op de leeftijd van 14 maanden vervangen door MenACWY-vaccinatie. Het percentage mensen dat aan MenW-ziekte overlijdt is aanzienlijk hoger (17 procent) dan bij andere meningokokken serogroepen.

In 2017 was het aantal meldingen van mazelen met 16 gevallen laag, maar wat hoger dan in voorgaande twee jaren. Het aantal meldingen van kinkhoest was in lijn met 2016 (28,7 vergeleken met 32,6 per 10.000). Er overleden drie mensen aan kinkhoest, één jonge zuigeling en twee ouderen. Het aantal meldingen van acute hepatitis B bleef stabiel (0,7 per 100.000 populatie). Ook het aantal mensen dat ziek werd van een type pneumokokkenziekte waartegen het vaccin beschermt, bleef erg laag in 2017/2018. Net als voorgaande waren er in 2017 weinig meldingen van bof (46), *Haemophilus influenzae* type b (Hib; 46), meningokokken serogroep C (MenC; 9), difterie (4), tetanus (1), rodehond (0) en polio (0).

De inwoners van Bonaire, St. Eustatius en Saba zijn overwegend goed beschermd tegen ziekten uit het RVP. Alleen de bescherming tegen mazelen en difterie is voor sommige leeftijdsgroepen niet optimaal. Alertheid is geboden om eventuele patiënten snel op te sporen om te voorkomen dat deze ziekten zich vanuit omliggende landen verspreiden. Daar zijn sinds kort uitbraken gaande.

Nieuwe adviezen en besluiten

In juli 2018 heeft de minister van Volksgezondheid, Welzijn en Sport (VWS) besloten om de MenACWY-vaccinatie vanaf oktober 2018 uit te bereiden naar 13-14- jarigen; in 2019 komt er een inhaalcampagne voor alle 15-18-jarigen. Ook is besloten om vaccinatie tegen het rotavirus aan te bieden aan risicogroepen en dat kinkhoestvaccinatie voor zwangeren via het RVP wordt georganiseerd door jeugdgezondheidszorg organisaties. De Gezondheidsraad adviseert vaccinatie tegen pneumokokken aan te bieden aan 60-plussers.

Kernwoorden: Rijksvaccinatieprogramma (RVP), difterie, *Haemophilus influenzae*, hepatitis B, human papillomavirus (HPV), mazelen, meningokokkenziekte, bof, kinkhoest, pneumokokkenziekte, polio, rodehond, tetanus, hepatitis A, respiratoir syncytieel virus (RSV), rotavirus, varicella zoster virus (VZV)

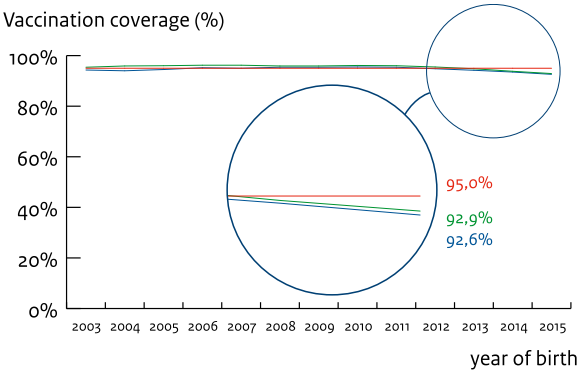
Vaccination coverage drops slightly again, HPV vaccination coverage drops considerably

Immunisation coverage and annual report National Immunisation Programme in the Netherlands 2017

Once again, fewer girls than last year received the vaccine against cervical cancer. Participation coverage for receiving the HPV vaccine decreased from 53 to 46 per cent. There was also a decrease in the vaccination coverage for other vaccinations that are part of the National Immunisation Programme. From an international perspective, vaccination coverage in the Netherlands is still high.

Figure 1: trend participation infants

(Vaccination coverage for the DTP and MMR vaccine at age 2 years)

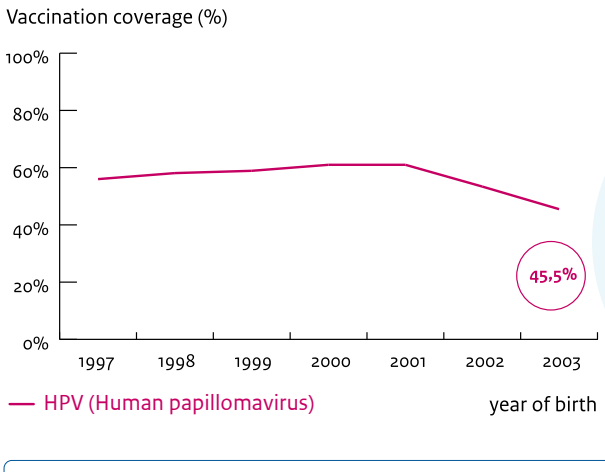


— Target World Health Organisation MMR (95%)
— MMR (Measles-Mumps-Rubella)
— DTaP-IPV (Diphtheria-Pertussis-Tetanus-Polio)

Since 1 January 2018, the youth health care division has taken more time to talk to parents about vaccination.

Figure 2: trend participation adolescent girls

(Vaccination coverage for the HPV vaccine at age 14 years)



The main reason for not being vaccinated against HPV, or to have misgivings about it, is concern about possible side effects of the HPV vaccine.

Read the report or read more on the National Immunisation Programme

Report →

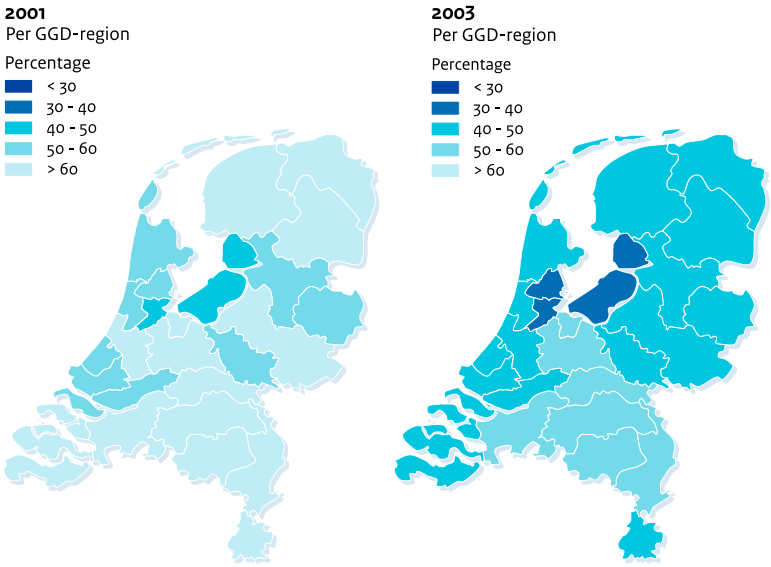
National Immunisation Programme →

Read more on the research results

Next page →

Figure 3: HPV vaccination coverage per Municipal Health Service (GGD) region - birth year 2001 versus 2003

Vaccination coverage in percentages for the HPV vaccine at age 14 years



More on herd immunity →

This is a publication by:

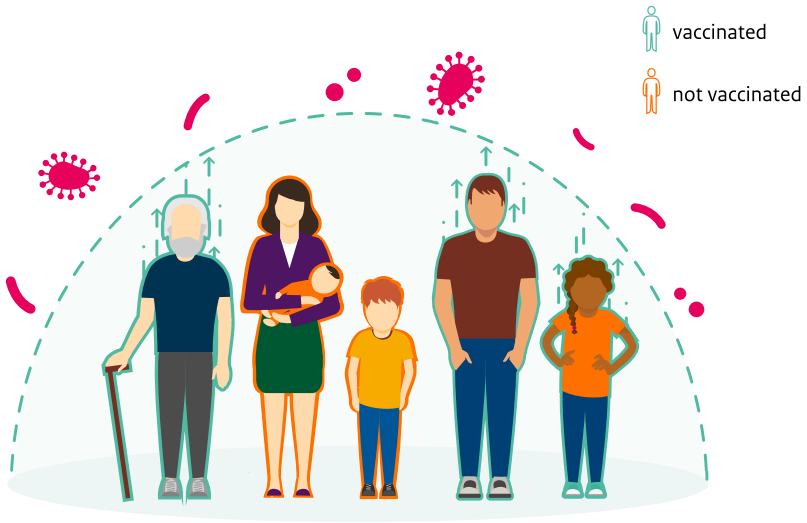
National Institute for Public Health and the Environment

P.O. Box 1 | 3720 BA Bilthoven

www.rivm.nl/rijksvaccinatieprogramma

June 2018

Figure 4: herd immunity protects young children and the most vulnerable



Proper protection by high vaccine coverage
For many infectious diseases there is herd immunity. This means that when a lot of children are vaccinated against a certain infectious disease, this disease is less likely to occur. Even children who haven't been vaccinated are at less risk of contracting the infectious disease. They are protected by the group of vaccinated children. To create and keep this herd immunity, it's important to have as many vaccinated children as possible. If nearly all children are vaccinated, a disease can disappear completely.

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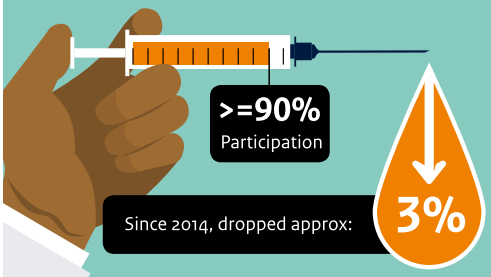
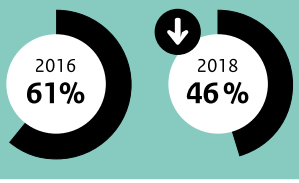
Committed to health and sustainability

Vaccination uptake

Participation in the Dutch National Immunisation Programme

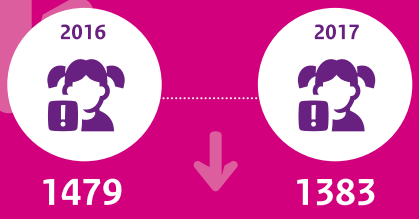


The participation in HPV vaccination declined with 15% since 2016.



Reported adverse events

following immunisation



HPV vaccination

Research shows **no association** between HPV vaccination and long-term fatigue symptoms

Highlights surveillance 2017 - 2018

Pathogen

Measles genotypes B3 and D8 were detected; these are the two genotypes most commonly found in other European countries

Disease

Hepatitis B
The number of reports of acute HepB infections (115) remained stable

Measles
16 reported cases, which exceeds previous years

Pertussis
3 people died: one infant and two elderly people

Immunosurveillance

Overall seroprotection in Caribbean Netherlands:

- Measles **94%**
- Diphtheria **78%**
- Mumps **85%**
- Rubella **85%**
- Tetanus **99%**

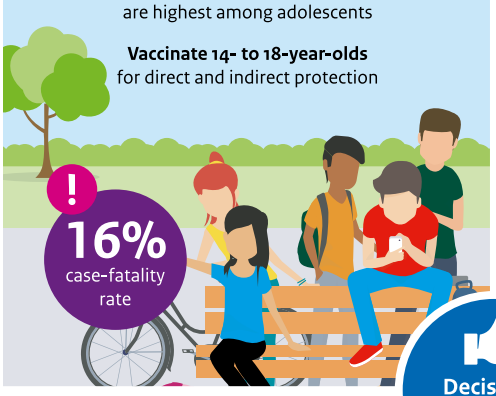
Meningococcal W

Increase in number of patients per year:

2015	2016	2017	2018
9	50	80	78 till aug

Carrier status and risk
are highest among adolescents

Vaccinate 14- to 18-year-olds
for direct and indirect protection



16% case-fatality rate

Rotavirus

Thousands of hospital admissions per year

Vaccination of risk groups is cost-effective

Eradication of mortality

Slight risk of serious side effects

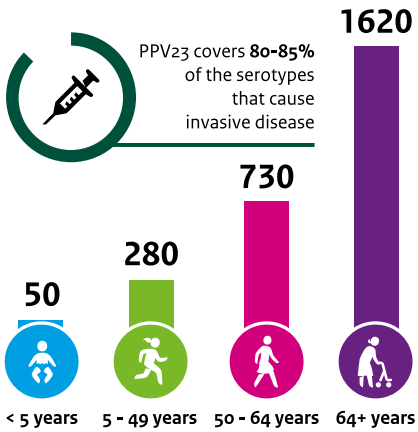
Decision
Vaccination for risk groups

Decisions Ministry of Health

Pneumococcal

Vaccination does not prevent all diseases caused by pneumococci, but it does reduce the number of hospital admissions and mortality

PPV23 covers **80-85%** of the serotypes that cause invasive disease



Provide vaccination against pneumococci to the elderly starting at 60 years of age

Maternal pertussis

- More than **90%** effective
- Protects the newborn
- Is safe

Preface

This report presents an overview of surveillance and developments in the period 2017–2018 that are relevant for the Netherlands with respect to diseases included in the current National Immunisation Programme (NIP): diphtheria, *Haemophilus influenzae* serotype b (Hib) disease, hepatitis B, human papillomavirus (HPV) infection, measles, meningococcal disease, mumps, pertussis, pneumococcal disease, poliomyelitis, rubella and tetanus. It also describes surveillance data concerning potential target diseases: hepatitis A infection, respiratory syncytial virus (RSV) infection, rotavirus infection, and varicella zoster virus (VZV) infection. In addition, it includes an overview of vaccines for infectious diseases undergoing clinical trials that are relevant for the Netherlands.

The report has the following structure:
Chapter 1 gives a short introduction of the NIP organisation. Recent results of vaccination coverage are discussed in Chapter 2. Chapter 3 focuses on the burden of diseases included in the NIP. Public acceptance of vaccination and the communication of the NIP are described in Chapter 4, while information on adverse events following immunisation (AEFI) is given in Chapter 5. In Chapter 6, various research topics that address the evaluation of the NIP in a broader sense are presented. These include the data collection in the third seroepidemiological study in the Netherlands, results of research of non-specific effects of vaccination, and a historical overview of government expenditure on vaccinations. Chapter 7 focuses on the current NIP target diseases. For each disease, the section starts with key points showing the most prominent findings, followed by figures and tables; thereafter an update of information on epidemiology, the pathogen, the results of current and ongoing studies, and international developments is given. Vaccination coverage and developments in the current NIP target diseases in the Caribbean Netherlands are presented in Chapter 8. Chapter 9 describes potential new target diseases that are under consideration for (future) vaccination implementation. Finally, in Chapter 10, an overview is given of vaccines for infectious diseases that are undergoing clinical trials and that are potentially relevant for the Netherlands.

In Appendix 1, the surveillance methods used to monitor the NIP are described. Appendix 2 reports on mortality and morbidity figures from 1997 onwards based on various data sources. Appendix 3 gives an overview of changes in the NIP since 2000, while Appendix 4 presents the composition of the vaccines used in the period 2016–2017. Appendix 5 gives an overview of recent publications by the National Institute for Public Health and the Environment (RIVM), and Appendix 6 lists relevant websites.

Comprehensive summary

The current National Immunisation Programme (NIP) includes vaccination agaist 12 vaccine preventables diseases (VPDs), e.g. diphtheria, pertussis, tetanus, poliomyelitis, *Haemophilus influenzae* disease, measles, mumps, rubella, meningococcal disease, hepatitis B, pneumococcal disease and human papillomavirus (HPV) infection (Figure 1). In this report surveillance data and scientific developments relevant for the Netherlands are presented with regard to these diseases as well as for potential new target diseases, i.e. rotavirus infection, varicella zoster virus (VZV) infection (varicella and herpes zoster), hepatitis A and respiratory syncytial virus (RSV) infection.

Current vaccination schedule

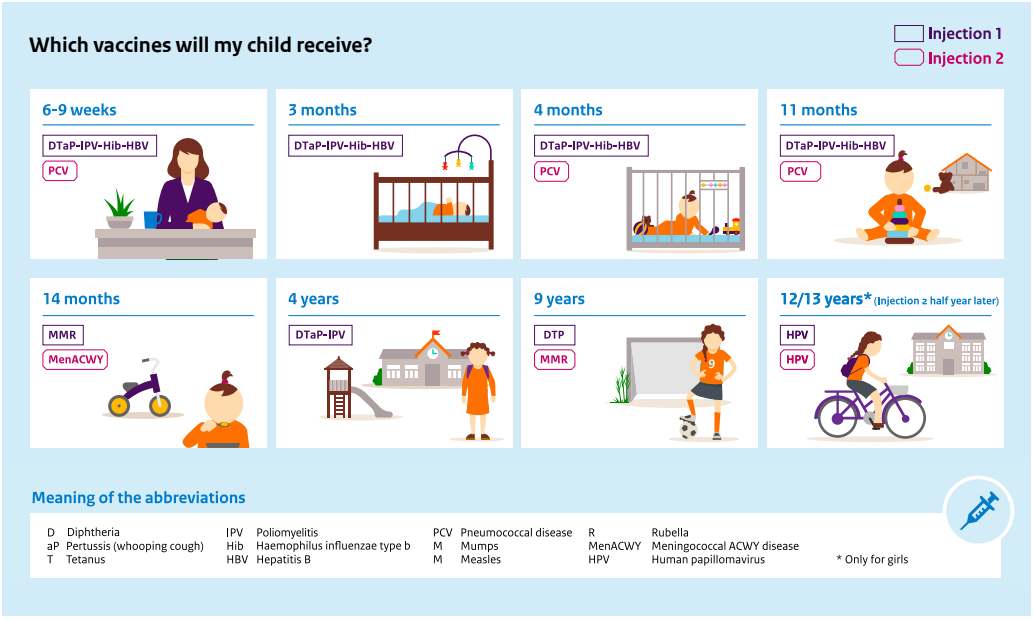
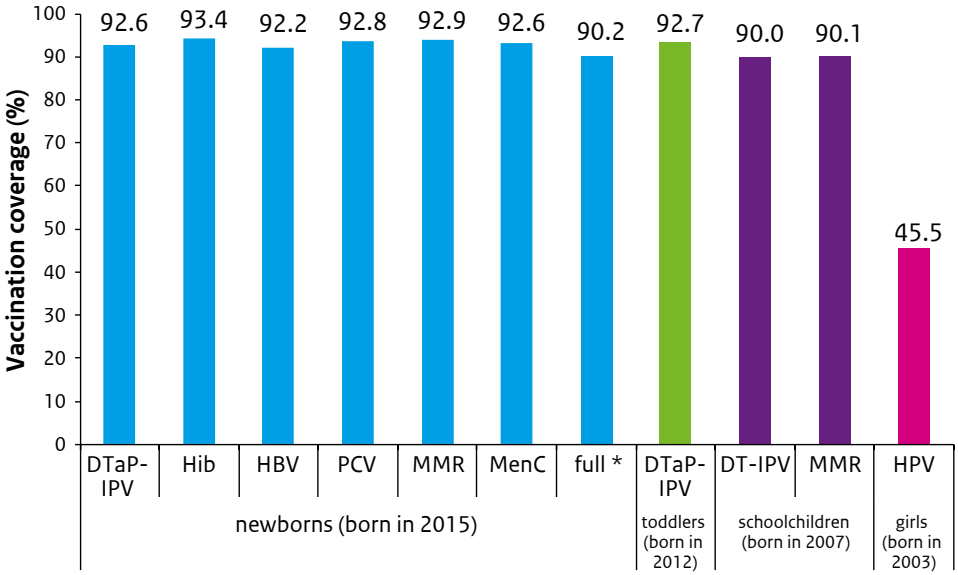


Figure 1 NIP Vaccination schedule
Source: *http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals*

Vaccination coverage

Vaccination coverage in the Netherlands is still high with the exception of HPV but has declined slightly in the period 2014 to 2018. Since 2014, the vaccination coverage for most vaccinations has now fallen by around 2-3%.
The HPV vaccination coverage has decreased by 15% since 2016, with a remarkable decline of 8% compared to last year. The main reasons given for having doubts about or for not vaccinating against HPV are concerns about the vaccine's possible side effects.



* full = all NIP vaccinations received according to schedule at 2 years of age.

Figure 2 Vaccination coverage per vaccine for newborns, toddlers, schoolchildren and adolescent girls in report year 2018
Source: Præventis

Acceptance of vaccination

Attitude and trust in vaccinations remained high among the group of parents who vaccinate their children. Side-effects, doubts about HPV-vaccine effectiveness, too little information, and negative stories about HPV vaccination were the most important reasons mentioned by parents regarding their decision not to vaccinate their daughters against HVP.
Adolescents and parents had a generally positive attitude and intention towards MenACWY vaccination. Among GPs and GP nurses the attitude towards need and effectiveness of vaccination in general was high, however it was somewhat lower for MenACWY vaccination and

HPV vaccination. Women at childbearing age were neutral/positive towards maternal pertussis vaccination, and providing information had a significant positive influence on their attitudes.

Burden of disease

The estimated disease burden caused by (partly) vaccine preventable diseases expressed in Disability Adjusted Life Years (DALY) for the year 2017 was lowest lowest for poliomyelitis, rabies and rubella (0 DALY/year) while it was highest for invasive pneumococcal disease (9,800 DALY/year), pertussis (2,000 DALY/year), invasive meningococcal disease (1,100 DALY/year), and rotavirus infection (1,100 DALY/year). In a separate analysis, the average annual disease burden for HPV in the period 2011–2014 was estimated at 13,800 DALY (76% among women), higher than the burden of any of the diseases mentioned above. Compared with the estimated burden in 2016, the burden in 2017 increased for invasive meningococcal disease, hepatitis A, rotavirus infection, and pertussis.

Adverse events

In 2017, Lareb received 1,383 reports with a total of 5,423 adverse events following immunisation (AEFI). Compared to 2016, the number of reports declined by 7%. As a result of change in recording in local site reactions, the number of registered AEFIs per report increased by 48%. No signal emerged to indicate that vaccines used in the NIP were unsafe.

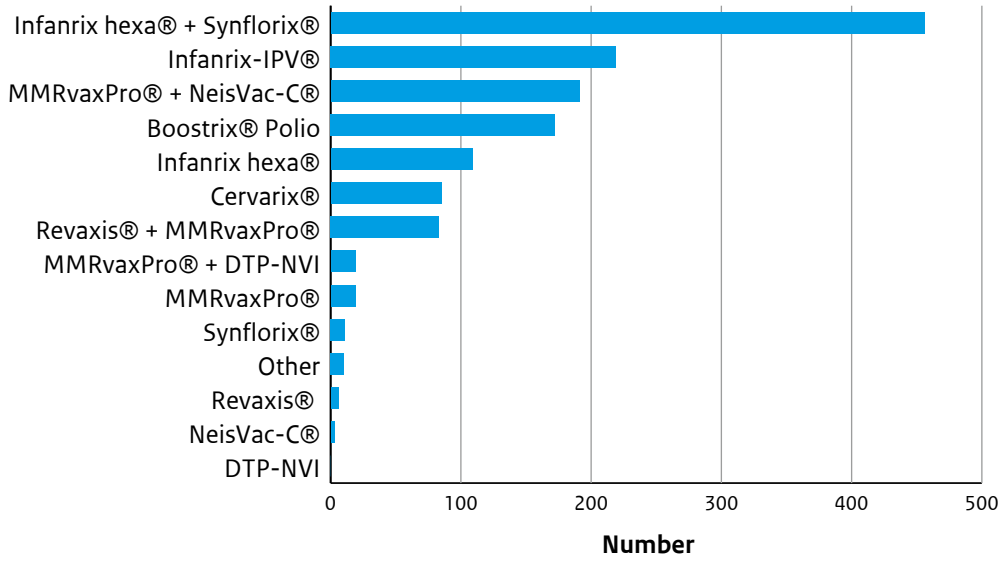


Figure 3 Number of reports of adverse events per suspected vaccine(s) in 2017
Source: Lareb

Various research topics addressing evaluation of the NIP in a broader sense

Immunosurveillance: PIENTER-3
Data collection of the third seroepidemiological study (PIENTER-3) ended in 2017. In total, 7,623 serum samples were collected. The response of PIENTER-3 (blood and questionnaire) was 14.4% for the national sample and 19.8% in the sample of low vaccination coverage areas. Almost half of the participants also donated oro- and nasopharyngeal swabs, faeces and completed an additional questionnaire.

Non-specific effects of vaccination
A lower rate of admission to hospital due to infections among children was observed; in the period after receipt of MMR vaccination this may be at least partly explained by a healthy vaccinee bias. The lower rate was associated with receipt of any additional vaccine, not specifically MMR vaccine.

Historical overview of government expenditure on vaccinations
The rising costs of vaccination programmes are an important point of discussion; a good understanding of the evolving expenses is important for current debates on the decision to include a new vaccine.

Current NIP

Diphtheria
In 2017, four notifications of diphtheria cases were received: cases were aged between 24-54 years (one unvaccinated and three vaccinated). In 2018 up to July 1, one notification has been received regarding a 32-year-old vaccinated male. A diphtheria outbreak is ongoing in three countries in the south and middle region of the Americas as result of decrease in vaccination coverage.

Haemophilus influenzae disease
The number of cases of *Haemophilus influenzae* type b (Hib) disease in 2017 (n=46) was similar to 2016 (n=44). Up to May 2018, 16 cases have been reported. In 2017, the incidence of Hib disease was highest among children aged under 5 years (1.6 per 100,000). In this age group, the incidence in 2017 was lower than in 2016 (2.4 per 100,000; n=21), so the increasing trend observed from 2011 to 2016 did not continue in 2017. In 2017, 11 Hib cases with vaccine failure (61% of all vaccine-eligible Hib cases) were reported, resulting in Hib vaccine effectiveness estimate of 93%, similar to previous years. In 2017, more cases of nontypeable Hi (NTHi) disease were reported than in 2016 (159 vs. 124). Up to May 2018, 91 cases have been reported; higher than in the same period in 2017 (80 cases) or 2016 (61 cases), confirming a continuing increase in NTHi disease.

Hepatitis B
Of the total number of 1,236 reported hepatitis B cases, 9% had an acute infection and 89% a chronic infection. The incidence of acute hepatitis B notifications remained stable in 2017 at 0.7 per 100,000 population. Among both men and women, heterosexual contact was the most frequently

reported risk factor for acute HBV infection. In 2017, genotype A continued to be the dominant genotype among acute HBV cases, with 62% of 76 genotyped cases, followed by genotype D (12%). After declining for seven consecutive years, the number of newly diagnosed chronic HBV infections increased by 12% in 2017 to 1,105, corresponding to an incidence of 6.5 per 100,000 population. Of people with a chronic HBV infection, 91% were born abroad. In contrast, 79% of people with an acute HBV infection were born in the Netherlands.

Human papillomavirus (HPV) infection

The incidence of cervical cancer increased in 2017 (8.91 per 100,000 compared to 8.32 per 100,000 in 2016), while the number of deaths slightly decreased (2.39 per 100,000 compared to 2.67 per 100,000 in 2016). In a prospective cohort study (HAVANA), high VE against vaccine types HPV16/18 was found for persistent infections up to seven years post-vaccination. In addition, significant cross-protection against persistent HPV infections by HPV31/45 was observed.
In 2015, the HPV16/18 prevalence among young STI clinic visitors decreased from 23% pre-vaccination (2009) to 15% among women, and from 17% pre-vaccination to 11% among heterosexual men (PASSYON study). Whole genome sequencing on HPV16 and HPV18 positive genital swabs revealed a large population of unique whole genome HPV16/18 variants. In persisting HPV16/18 infections, strong conservation of the virus within hosts was observed.
In a retrospective cohort study, no increased incidence rates for chronic fatigue syndrome were found post-vaccination. Moreover, there was no evidence for elevated risk of certain fatigue >=6m in the high-risk period of 12 months after vaccination.
In 2018, the Health Council is preparing a new advice on HPV-vaccination in the Netherlands.

Measles

In 2017, the number of reported measles cases (16) was low but higher than in the previous two years. In the first six months of 2018, 17 cases were reported, of which five in children were too young to be vaccinated. Genotypes B3 and D8 were detected; these are the two genotypes most commonly found in other European countries.

Meningococcal disease

The number of cases with meningococcal serogroup C (MenC) disease has consistently declined to low levels since introduction of vaccination, with only nine cases reported in 2017. There is an ongoing increase in the number of cases with meningococcal serogroup W (MenW) disease caused by a hypervirulent clonal complex 11 strain, with 80 cases reported in 2017 and 78 in the period to August 2018. As a result of this increase, since May 2018, the MenC vaccination given at 14 months of age has been replaced by a quadrivalent MenACWY vaccination. From October 2018, 13-14 year olds will be offered MenACWY vaccination. In 2019, there will be a catch up campaign for all 15-18 year olds. MenW disease occurs across all age groups, with peaks in incidence in <2 year olds and 14-24 year olds, and with an increasing incidence with age from 45-50 years. The case fatality of MenW disease from January 2015 to August 2018 was 17%, which is substantially higher than for other serogroups.
In 2018 (up to August), the incidence of meningococcal serogroup B (MenB) disease was lower than for MenW disease, although in children aged under 5, the incidence of MenB disease is still higher than for MenW disease, and has increased slightly since 2015.

The number of cases of meningococcal disease caused by serogroup Y or other serogroups is low and stable.

Mumps

The incidence of mumps in 2017 was low with 46 reported cases, and slightly lower than in the previous two years. Most of the mumps cases in the Netherlands were caused by mumps virus genotype G.

Pertussis

The 2017 pertussis incidence follows its long-term epidemiological pattern.. Pertussis incidence in 2017 amounted to 28.7 per 100,000 compared with 32.6 in 2016. Three persons died from pertussis, one infant and two elderly. The prevalence of pertactin-deficient (i.e. a component of acellular vaccines) strains was 9.7% in 2017, compared to 12% in 2016. The Ministry of Health, Welfare and Sport decided to offer maternal pertussis vaccination to all pregnant women, starting in 2019, to protect infants too young to be vaccinated against severe pertussis.

Pneumococcal disease

Introduction of pneumococcal conjugate vaccination (PCV) led in 2006 to a significant decrease in overall invasive pneumococcal disease (IPD) in children aged under 5, 5 to 49 year olds, and in those aged 65 and older. The incidence of PCV7 type invasive pneumococcal disease (IPD) remained very low in 2017/2018 with an incidence of 0.7 per 100,000. The incidence of PCV10-7 (i.e. PVC10 minus PCV7) type IPD further decreased in 2017/2018 to an incidence of 0.9 per 100,000. Vaccine effectiveness (VE) of at least two doses of PCV10 was 90% (95%CI 68-97%) against vaccine type IPD. The increasing trend in incidence of non-PCV10 type IPD continued in 2017/2018. The incidence of PCV13-10 type IPD (3.9/100,000), including serotype 19A, was significantly higher than before introduction of PCV7 (118% increase) and PCV10 (59% increase), and also higher than the incidence in 2016/2017 (3.2/100,000).
The incidence of PPV23-PCV13 type IPD in the 65+ age group has increased steadily from 10.6 per 100,000 in 2004/2005 to 24.4 per 100,000 in 2017/2018. Serotype 8, 19A, 3, 22F and 9N were the most common non-vaccine serotypes causing IPD in 2016/17. In 2018, the Health Council advised to offer pneumococcal vaccination to people aged 60 years and older.

Poliomyelitis

No cases of poliomyelitis were reported in 2017 and in the period up to 1 July 2018. However, worldwide eradication of polio is threatened by several outbreaks of VDPVs in non-endemic countries.

Rubella

No cases of rubella were reported in 2017 and in the first six months of 2018.

Tetanus

In 2017, one case of tetanus was reported. It concerned an elderly woman with unknown vaccination status who was not eligible for routine NIP vaccination. According to LCI guidelines

she should have been offered Tetanus Toxoid and anti Tetanus Immunoglobulines, but she only received Tetanus Toxoid as post-exposure prophylaxis. No cases were reported in 2018 up to July 1.

The immunisation programme in Caribbean Netherlands

In general, vaccination coverage in the Caribbean Netherlands is high. In Bonaire, at the end of 2016 and the beginning of 2017, some cases of whooping cough were reported, and in 2013 a single Hib case. Annually, an average of two cases with hepatitis B have been reported in recent years. In Saba, no cases of NIP diseases were diagnosed in 2017. From 2013 to 2017 in Aruba, 272 reports of vaccine preventable diseases (VPDs) were received, of which most concerned hepatitis B infection (64.0%).
From May-June 2017, sampling for the Health Study Caribbean Netherlands (HSCN) was conducted on the Dutch Caribbean Islands of Bonaire, St. Eustatius and Saba. Overall, 1,900 people were enrolled in the study, of which 1,197 (26%) on Bonaire, 480 (23%) on St. Eustatius, and 223 (22%) on Saba. First results indicate overall seroprevalences of 94% for measles, 85% for mumps, 85% for rubella, 78% for varicella, 78% for diphtheria, 10% for pertussis and 99% for tetanus.

Potential NIP target diseases

Hepatitis A

An international outbreak of hepatitis A among MSM, ongoing since July 2016, has also affected the Netherlands. In 2017, 374 hepatitis A cases were reported, of which 243 were related to the outbreak. For every two MSM cases, one person from the general population was infected. Of the remaining cases, 92 were unrelated to this outbreak, and 39 could not be assigned as no strain information was available.

Respiratory syncytial virus (RSV) infection

A total of 75 RS-viruses (6%) were detected in 1,236 combined nose swabs and throat swabs of influenza like illness (ILI) and other acute respiratory infections (ARI) patients, collected by sentinel GPs in the 2017/2018 respiratory season, compared with 12% in the season 2016/2017 and 5.0%-8.6% in the seasons 2012/2013 - 2015/2016.
As part of the RESCEU project, the RIVM has developed a novel RSV pentaplex immuno assay (RSV-MIA).

Rotavirus infection

As expected, 2017 showed an average rotavirus epidemic (n=1,047), supporting the hypothesis of a biennial pattern of rotavirus in the Netherlands. However, in contrast to this hypothesis, observations for 2018 up to week 19 show a similar pattern to those seen previously in the low season. G3P[8] was the most prevalent genotype in 2017.
The Ministry of Health, Welfare and Sport has decided to vaccinate high-risk group infants against rotavirus through the NIP.

Varicella zoster virus (VZV) infection (varicella and herpes zoster)

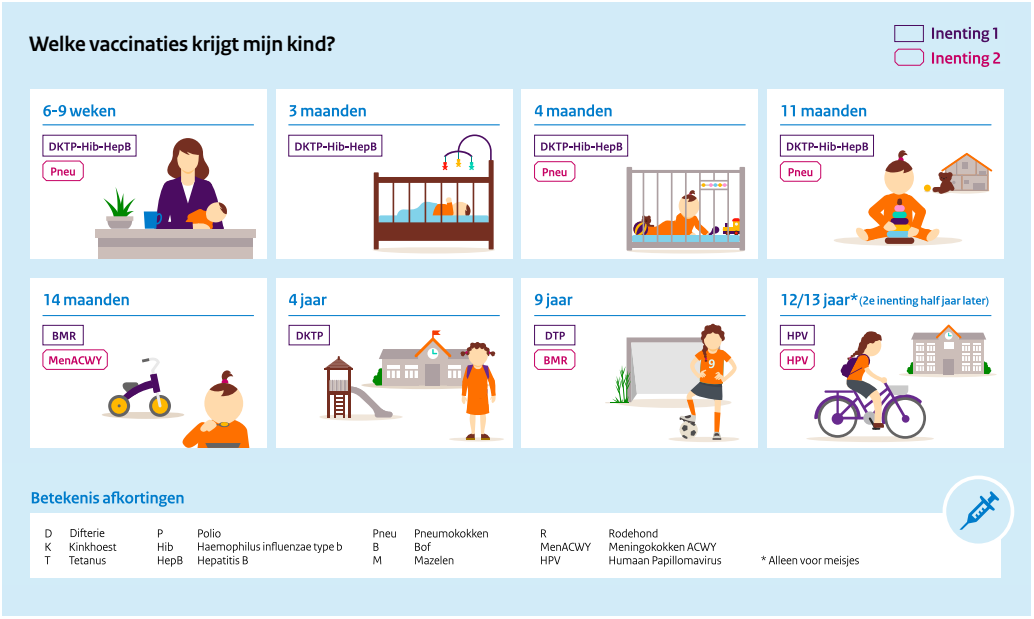
The VZV epidemiology (incidence of GP consultations, and deaths) in the Netherlands has not changed in recent years and is comparable to that of previous years; in 2016 GPs recorded 240 varicella and 530 herpes zoster episodes per 100,000 population.

In 2018, Shingrix®, a subunit vaccine, was registered for the prevention of herpes zoster (HZ). In a recent cost-effectiveness analysis for the Netherlands, Shingrix® was found to be superior in reducing the burden of HZ compared to Zostavax® alternatives, however the cost-effectiveness depended largely on the vaccine price.

Uitgebreide samenvatting

Het huidige Rijksvaccinatieprogramma (RVP) omvat vaccinatie tegen 12 ziekten, namelijk difterie, kinkhoest, tetanus, polio, *Haemophilus influenzae*-ziekte, mazelen, bof, rodehond, meningokokkenziekte, hepatitis B, pneumokokkenziekte en infectie met humaan papillomavirus (HPV; Figuur 1). In dit rapport worden surveillancedata en wetenschappelijke ontwikkelingen beschreven voor deze ziekten en voor ziekten waarvoor een vaccin (nog) niet in het RVP is opgenomen, zoals rotavirusinfectie, infectie met varicella zoster-virus (VZV; waterpokken en gordelroos), hepatitis A en infectie met respiratoir syncytieel virus (RSV).

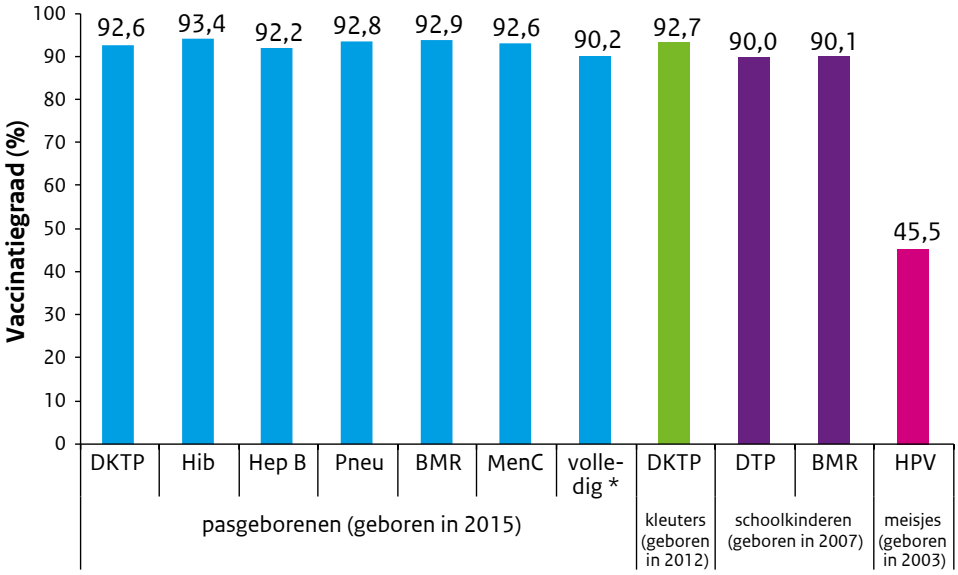
Huidig vaccinatieschema



Figuur 1 Vaccinatieschema van het RVP
Bron: *http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals*

Vaccinatiegraad

De vaccinatiegraad in Nederland is nog steeds hoog, ondanks de lichte daling in de periode 2014 tot 2018. De participatie voor de meeste vaccinaties is in totaal gedaald met ongeveer 2-3%. Een uitzondering op de hoge deelname is het aantal meisjes dat zich heeft laten vaccineren tegen HPV. De vaccinatiegraad voor HPV-vaccinatie is gedaald met 15% sinds 2016. De daling met 8% in het laatste jaar is opvallend. De belangrijkste reden om niet te vaccineren tegen HPV of hierover te twijfelen is zorgen over mogelijke bijwerkingen van het HPV-vaccin.



* volledig = alle RVP-vaccinaties volgens schema ontvangen op 2-jarige leeftijd.

Figuur 2 Vaccinatiegraad per vaccin voor pasgeborenen, kleuters, schoolkinderen en adolescente meisjes in verslagjaar 2018
Bron: Præventis

Acceptatie van vaccinatie

Onder ouders die hun kinderen laten vaccineren is de houding en het vertrouwen in vaccinaties nog steeds hoog. Bijwerkingen, twijfels over de effectiviteit van HPV-vaccinatie, te weinig informatie en negatieve verhalen over HPV-vaccinatie waren de belangrijkste redenen voor ouders om hun dochters niet te laten vaccineren tegen HPV.
Adolescenten en ouders hadden een positieve houding en intentie tegenover MenACWY-vaccinatie. Onder bezoekers van de huisartsenbeurs was het belang en de effectiviteit van vaccinatie over het algemeen hoog, maar iets lager voor MenACWY-vaccinatie en HPV-vaccinatie. Vrouwen op vruchtbare leeftijd waren neutraal/positief tegenover maternale kinkhoestvaccinatie en het geven van informatie had een significant positieve invloed op de houding van vrouwen.

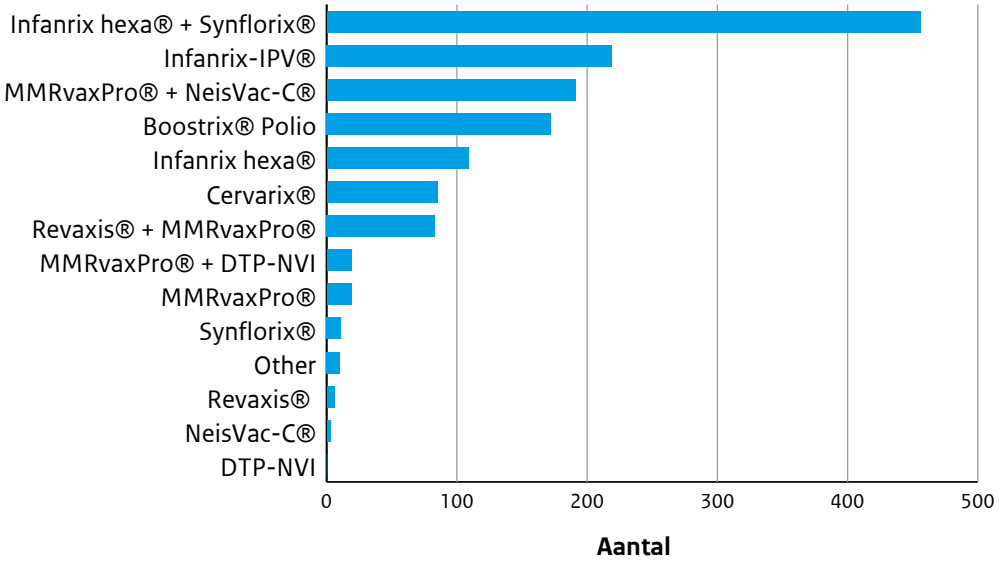
Ziektelast

De geschatte ziektelast veroorzaakt door ziekten die (deels) door vaccinatie te voorkomen zijn, uitgedrukt in *Disability Adjusted Life Years* (DALY), was in 2017 het laagst voor polio, rabies en rubella (0 DALY/jaar) en het hoogst voor: invasieve pneumokokkenziekte (9.800 DALY/jaar), kinkhoest (2.000 DALY/jaar), invasieve meningokokkenziekte (1.100 DALY/jaar) en

rotavirusinfectie (1.100 DALY/jaar). De gemiddelde jaarlijkse ziektelast voor HPV in de periode 2011-2014, geschat in een aparte analyse, was met 13.800 DALY (76% voor vrouwen) hoger dan voor alle bovengenoemde ziekten. De geschatte ziektelast in 2017 was relatief hoog voor meningokokkenziekte, hepatitis A, rotavirus-infectie en kinkhoest, vergeleken met de geschatte ziektelast in 2016.

Bijwerkingen

In 2017 ontving Bijwerkingencentrum Lareb 1383 meldingen van in totaal 5423 mogelijke bijwerkingen van vaccins. In vergelijking met 2016 is het aantal meldingen gedaald met 7%. Door een verandering in registratie van lokale reacties vanaf januari 2017 is het aantal geregistreerde mogelijke bijwerkingen na vaccinatie per melding gestegen met 48%. Er zijn geen signalen naar voren gekomen die erop wijzen dat vaccins die in het RVP worden gebruikt, niet veilig zouden zijn.



Figuur 3 Aantal meldingen van mogelijke bijwerkingen per vaccin(s) in 2017
Bron: Lareb

Verschillende onderzoeksonderwerpen over de evaluatie van het RVP in bredere zin

Immuun surveillance: PIENTER-3

Datacollectie van de derde nationale sero-epidemiologische studie (PIENTER3) eindigde in 2017. In totaal zijn er 7.623 serummonsters verzameld. De respons was 14,4% (bloed en vragenlijst) voor de nationale steekproef en 19,8% voor de steekproef in de lage-vaccinatiegraad-gemeenten. Ongeveer de helft van de deelnemers hebben ook oro- en nasopharyngale swabs, feces en een extra vragenlijst ingeleverd.

Niet-specifieke effecten van vaccinatie

Na BMR-vaccinatie werd minder vaak een ziekenhuisopname met een infectie geobserveerd. Dit kon (deels) worden verklaard door vertekening veroorzaakt doordat gezonde kinderen zich mogelijk beter volgens de richtlijnen laten vaccineren (‘*healthy vaccinee bias*’). De lagere geobserveerde ziekenhuisopname was geassocieerd met de ontvangst van elk ander vaccin, niet specifiek BMR.

Historisch overzicht van overheid kosten aan vaccinaties

De stijgende kosten van vaccinatieprogramma’s zijn een belangrijk discussiepunt. Een goed begrip van deze evoluerende uitgaven is belangrijk voor de huidige debatten over het introduceren van een nieuw vaccin of niet.

Huidig RVP

Difterie

In 2017 zijn er vier patiënten gemeld met difterie. Zij waren tussen 24-54 jaar In de eerste helft van 2018 is een difteriemelding ontvangen van een gevaccineerde 32-jarige persoon. In Zuid- en Midden Amerika zijn in drie landen uitbraken van difterie gaande door sterke achteruitgang van de vaccinatiegraad.

Haemophilus influenzae-ziekte

Het aantal gevallen van invasieve ziekte veroorzaakt door *Haemophilus influenzae* type b (Hib) in 2017 (n=46) was vergelijkbaar met het aantal in 2016 (n=44). Tot en met mei 2018 werden er zestien gevallen van Hib gemeld. In 2017 werd de hoogste incidentie gevonden onder kinderen jonger dan vijf jaar (1,6 per 10.000). In deze leeftijdsgroep was de incidentie in 2017 lager dan in 2016 (2,4 per 100.000; n=21); de toename die zichtbaar was van 2011 tot 2016 werd daarmee niet voortgezet in 2017. Er waren elf Hib-vaccinfalens in 2017 (61% van alle Hib-cases die in aanmerking kwamen voor vaccinatie), wat resulteerde in een schatting van de vaccineffectiviteit (93%), vergelijkbaar met voorgaande jaren. Het aantal gevallen veroorzaakt door een niet-typeerbare Hi-stam was hoger in 2017 dan in 2016 (159 vs. 124). Tot en met mei 2018 werden al 91 gevallen gemeld, wat hoger is dan in dezelfde periode in 2017 (80 gevallen) en 2016 (61 gevallen); dit bevestigt de toename in Hi door een niet-typeerbare stam.

Hepatitis B

In totaal werden 1.236 hepatitis B-meldingen gedaan, waarvan 9% met een acute en 89% met een chronische infectie. De incidentie van acute hepatitis B bleef met 0,7 meldingen per 100.000 populatie stabiel in 2017. Onder zowel mannen als vrouwen was heteroseksueel contact de meest gerapporteerde risicofactor voor een acute hepatitis B-infectie. Genotype A bleef met 62% van de 76 getypeerde cases het meest dominante genotype onder acute cases in 2017, gevolgd door genotype D met 12%.

Na een daling in zeven opeenvolgende jaren is het aantal nieuw gediagnostiseerde chronische hepatitis B-infecties gestegen met 12% in 2017 tot 1.105 (incidentie 6,5 per 100.000 populatie). Van de patiënten met een chronische hepatitis B-infectie was 91% in het buitenland geboren. Van de acute hepatitis B-patiënten is 79% in Nederland geboren.

Human papillomavirus (HPV)-infectie

De incidentie van baarmoederhalskanker is toegenomen in 2017 (8,91 per 100.000 vergeleken met 8,32 per 100.00 in 2016), terwijl het aantal sterfgevallen licht daalde (2,39 per 100.000 vergeleken met 2,67 per 100.00 in 2016). In een prospectieve cohortstudie (HAVANA) werd een hoge vaccineffectiviteit gevonden tegen persisterende infecties met HPV-vaccin-typen 16/18, tot in ieder geval zeven jaar na de vaccinatie. Ook werd significante kruisbescherming gevonden tegen persisterende infecties met HPV 31/45.

De prevalentie van HPV16/18 onder jonge SOA-polibezoekers is afgenomen van 23% voor de invoering van vaccinatie (2009) tot 15% in 2015 voor vrouwen en van 17% voor de invoering van vaccinatie naar 11% in mannen (PASSYON-studie). *Whole genome sequencing* van genitale swabs die positief zijn voor HPV16 of HPV18 heeft een grote diversiteit aan unieke HPV16/18-genoomvarianten aangetoond. Tevens bleek dat in persisterende HPV16/18-infecties, er sterke conservatie is van het virus in de gastheer.

In een retrospectieve cohortstudie werden geen verhoogde incidentieratio's gevonden voor het chronisch-vermoeidheid-syndroom na vaccinatie. Tevens werd geen verhoogd risico gevonden voor vermoeidheid ≥6 maanden in de hoog-risico-periode van twaalf maanden na vaccinatie.

In 2018 is de Gezondheidsraad een nieuw advies over HPV vaccinatie aan het voorbereiden.

Mazelen

In 2017 was het aantal meldingen van mazelen laag (16), maar hoger dan in voorgaande twee jaren. In de eerste zes maanden van 2018 zijn er zeventien gevallen gerapporteerd, waarvan vijf kinderen die de vaccinatieleeftijd nog niet hadden bereikt. Genotype B3 en D8 werden gedetecteerd. Deze genotypen werden ook het meest gevonden in andere Europese landen.

Meningokokkenziekte

Het aantal gevallen van meningokokken serogroep C (MenC)-ziekte is nog steeds erg laag, met slechts negen gerapporteerde gevallen in 2017.

In 2017 en 2018 was er een aanhoudende stijging in het aantal gevallen van meningokokken W (MenW)-ziekte veroorzaakt door een hypervirulent type (cc11) met 80 gevallen in 2017 en 78 in 2018 tot en met augustus. Vanwege deze toename is sinds mei 2018 de MenC-vaccinatie op de leeftijd van veertien maanden vervangen door MenACWY-vaccinatie. Vanaf oktober 2018

wordt MenACWY-vaccinatie aangeboden aan 13-14-jarigen en in 2019 zal er een inhaalcampagne zijn voor alle 15-18-jarigen. MenW-ziekte komt bij alle leeftijden met pieken in de incidentie bij kinderen <2 jaar en 14-24-jarigen. Vanaf 45-50 jaar neemt de incidentie toe met de leeftijd. In de periode januari 2015 tot en met augustus 2018 was het overlijdenspercentage van MenW-ziekte 17%; dit is aanmerkelijk hoger dan voor andere serogroepen.
In 2018 (tot en met augustus) was de incidentie van meningokokken-serogroep B (MenB)-ziekte lager dan van MenW-ziekte. In kinderen <5 jaar is de incidentie van MenB-ziekte echter nog steeds hoger dan die van MenW-ziekte, en deze is ook licht aan het stijgen sinds 2015.
Het aantal gevallen van meningokokkenziekte door serogroep Y en andere serogroepen is laag en stabiel.

Bof
De incidentie van bof was in 2017 laag (46 meldingen) en daarmee iets lager dan in de voorgaande twee jaar. De meeste gevallen van bof worden veroorzaakt door genotype G.

Kinkhoest
In 2017 was de incidentie per 100.000 van kinkhoestmeldingen in lijn met de gebruikelijke epidemiologie en bedroeg 28,7 vergeleken met 32,6 in 2016. Drie mensen (één jonge zuigeling en twee ouderen) zijn overleden aan kinkhoest. Het percentage pertactine-deficiënte stammen was 9,7% in 2017, vergeleken met 12% in 2016. De Minister van Volksgezondheid, Welzijn en Sport heeft besloten alle zwangere vrouwen een kinkhoestvaccinatie aan te bieden. Dit programma start in 2019 om zuigelingen die nog te jong zijn voor vaccinatie te beschermen.

Pneumokokkenziekte
Introductie van pneumokokkenvaccinatie (PCV) in 2006 heeft geleid tot een significante daling in invasieve pneumokokkenziekte onder kinderen jonger dan vijf jaar, onder 5- tot 49-jarigen en onder ouderen van 65 jaar of ouder. De incidentie van PCV7-typen pneumokokkenziekte bleef met 0,7 per 100.000 erg laag in 2017/2018. The incidentie van pneumokokkenziekte veroorzaakt door de additionele typen in PCV10 (serotype 1, 5 en 7F) daalde verder in 2017/2018 naar een incidentie van 0,9 per 100.000. De vaccineffectiviteit van minimaal twee doses PCV10 was 90% (95%BI 68-97%) tegen pneumokokkenziekte veroorzaakt door vaccintypen.

De incidentie van niet-PCV10-typen steeg verder in 2017/2018. De incidentie van pneumokokkenziekte veroorzaakt door additionele typen in PCV13 (3,9 per 100.000), inclusief serotype 19A, was significant hoger in 2017/2018 dan vóór introductie van PCV7 (118% stijging) en PCV10 (59% stijging), en hoger dan de incidentie in 2016/2017 (3,2 per 100.000).

De incidentie van pneumokokkenziekte veroorzaakt door additionele typen in PPV23 in personen van 65 jaar en ouder steeg gestaag over de laatste jaren, van 10,6 per 100.000 in 2004/2005 naar 24,4 per 100.000 in 2017/2018.
De Gezondheidsraad adviseert vaccinatie tegen pneumokokken aan te bieden aan 60-plussers.

Polio
In 2017 en 2018 tot 1 juli zijn er geen meldingen van poliomyelitis gedaan. De eradicatie van polio wordt bedreigd door verschillende uitbraken van VDPV's in landen waar polio niet meer endemisch is.

Rodehond
In 2017 en de eerste zes maanden van 2018 werden geen gevallen van rodehond gerapporteerd.

Tetanus
In 2017 is er één melding van tetanus ontvangen. Het betrof een oudere vrouw, die vanwege haar leeftijd niet in aanmerking kwam voor deelname aan het RVP. Volgens de LCI richtlijnen had zij behandeld moeten worden met Tetanus Toxoid en anti Tetanus Immunoglobulines, maar zij ontving als behandeling uitsluitend Tetanus Toxoid. In 2018 zijn er tot 1 juli geen meldingen van tetanus gedaan.

Het vaccinatieprogramma in Caribisch Nederland

Over het algemeen is de vaccinatiegraad in Caribisch Nederland hoog. In Bonaire werd aan het eind van 2016 en begin 2017 een aantal gevallen van kinkhoest gerapporteerd. Ook worden in de meest recente jaren gemiddeld twee personen per jaar met hepatitis B gerapporteerd. In Saba werden in 2017 geen gevallen gerapporteerd van ziekten die in het RVP zitten. In Aruba werden vanaf 2013 tot en met 2017 272 gevallen van door vaccinatie te voorkomen ziekten gemeld, waarbij het voornamelijk hepatitis B betrof (64,0%).
In mei-juni 2017 vond bemonstering voor de Health Studie Caribisch Nederland (HSCN) plaats op Bonaire, St. Eustatius en Saba. In totaal werden 1.900 mensen (25%) geïncludeerd in de studie, waarvan 1.197 (26%) op Bonaire, 480 (23%) op St. Eustatius en 223 (22%) op Saba. Eerste resultaten laten een overall seroprevalentie zien van 94% voor mazelen, 85% voor bof, 85% voor rodehond, 78% voor difterie, 10% voor kinkhoest en 99% voor tetanus.

Potentiële RVP-kandidaten

Hepatitis A
Sinds juli 2016 is er een internationale uitbraak van hepatitis A gaande onder mannen die seks hebben met mannen, die ook in Nederland tot een sterke toename van hepatitis A heeft geleid. In 2017 zijn er 374 patiënten met hepatitis A gemeld, waarvan er 243 aan de uitbraak gerelateerd zijn. Op elke twee MSM-patiënten met hepatitis A was er ook één patiënt in de algemene bevolking. Van de overige patiënten waren 92 patiënten niet gerelateerd aan de uitbraak en was bij 39 patiënten onduidelijk of ze wel of niet bij de uitbraak hoorden door het ontbreken van een isolaat voor typering.

Respiratoir syncytieel virus (RSV)-infectie

In seizoen 2017/2018 werd het RS-virus in totaal 75 keer gevonden (6%) in 1236 neus- en keel-uitstrijken bij mensen met influenza-achtig ziektebeeld of een acute respiratoire infectie, verzameld door een groep huisartsen, vergeleken met 12% in het seizoen 2016/2017 en 5-9% in de seizoenen 2012/2013 - 2015/2016.

Als onderdeel van het RESCUE-project heeft het RIVM een nieuwe pentaplex immuno-essay (RSV-MIA) ontwikkeld.

Rotavirusinfectie

Zoals verwacht werd in 2017 een gemiddelde rotavirus-epidemie geobserveerd (n=1,047). Dit ondersteunt de hypothese van een tweejaarlijks epidemisch patroon in Nederland. Toch werd, in tegenstelling tot deze hypothese, in 2018 tot en met week 19 een vergelijkbaar patroon gezien als in de jaren voor lage seizoenen. G3P[8] was het meest prevalente genotype in 2017. De Minister van Volksgezondheid, Welzijn en Sport heeft besloten om zuigelingen met een hoog risico te vaccineren tegen rotavirus via het RVP.

Varicella zoster virus (VZV)-infectie (waterpokken en gordelroos)

De epidemiologie van VZV (huisartsenbezoeken, ziekenhuisopnames en sterfgevallen) is vergelijkbaar met voorgaande jaren: in 2016 huisartsen rapporteerden 240 waterpokken en 530 gordelroos gevallen per 100.000 populatie.

Het subunit-vaccin Shingrix® is geregistreerd in 2018 voor de preventie van herpes zoster (HZ). In een recente kosteneffectiviteitsanalyse voor Nederland was dit vaccin superieur in het verminderen van de ziektelast van HZ in vergelijking met Zostavax®-alternatieven, maar de kosteneffectiviteit hangt grotendeels af van de vaccinprijs.

1
Introduction

1.1 NIP vaccination schedule

Vaccination of a large part of the population of the Netherlands against diphtheria, tetanus and pertussis (DTP) was introduced in 1952. The National Immunisation Programme (NIP) started in 1957, offering DTP and inactivated polio vaccination (IPV) in a programmatic approach to all children born from 1945 onwards. Nowadays, in addition to DTP-IPV, vaccinations against measles, mumps, rubella (MMR), *Haemophilus influenzae* serotype b (Hib), meningococcal disease, invasive pneumococcal disease, hepatitis B virus (HBV) and human papillomavirus (HPV) are included in the programme (Figure 1.1). In the Netherlands, NIP vaccinations are administered to the target population free of charge and on a voluntary basis.

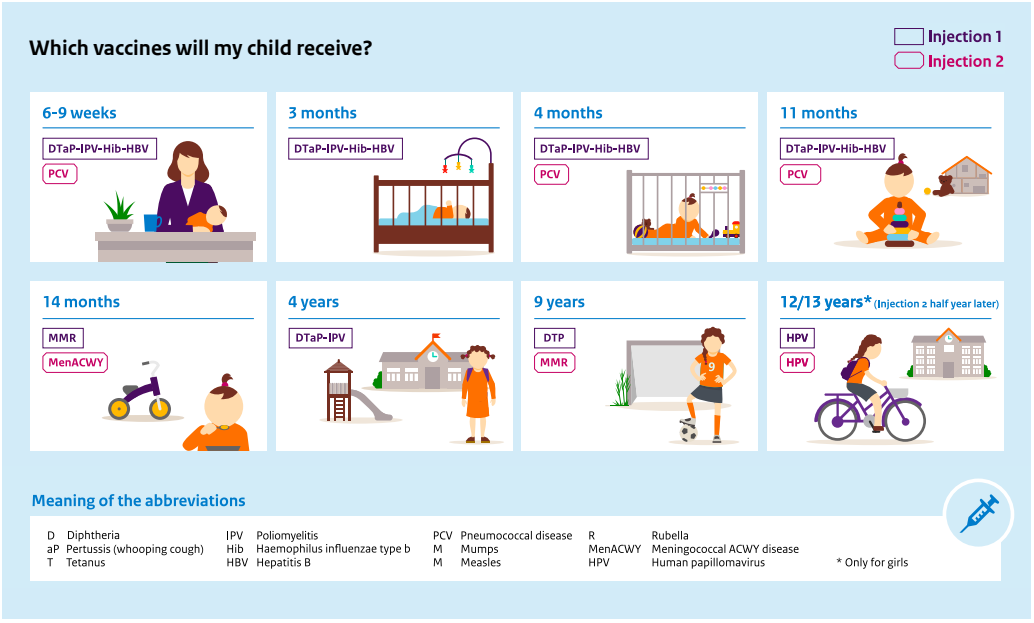


Figure 1.1 NIP vaccination schedule
Source: http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals

1.1.1 Changes in vaccination schedule

In 2017, no changes were made to the NIP vaccination schedule. From May 1, 2018, a MenACWY vaccine replaced the MenC vaccine at 14 months of age. In October 2018, adolescents born between May 1 2004 and December 31 2004 will be offered MenACWY vaccination.

1.1.2 Number of vaccinated children

In 2017, approximately 760,000 children aged 0 to 19 years were immunised in the context of the Dutch NIP. They received a total of 2,140,000 vaccine doses. In 2017, the vaccination schedule consisted of 12 (boys) or 14 (girls) vaccine doses per child. Of these, 7 were given between 0 and 11 months.

1.2 New advice and decisions

In 2015, the Dutch Health Council expanded the evaluation of non-NIP available vaccines and provided advice on them [1] to the Minister of Health, Welfare and Sport, who is responsible for deciding how vaccines are made available. Some vaccines will be included in a public vaccination programme.
In July 2018, the Secretary of State responsible for the NIP decided to expand the MenACWY vaccination outbreak programme. Next year, all 14-18 year-olds (birth cohorts 2001-2005) will have the opportunity to be vaccinated. Furthermore, the Secretary of State decided that vaccination against rotavirus-caused diseases will only be included in the NIP for infants at risk, and that NIP maternal pertussis vaccination will be introduced and will be organised by the youth health care organisations. The Health Council also advised in 2018 to offer pneumococcal vaccination to people 60 years and older.
Currently, the Health Council is preparing advice about HPV vaccination for boys, meningococcal vaccination (e.g. MenB, MenACWY for adolescents in NIP), and about adaptation of the vaccination schedule for infants in relation to maternal pertussis vaccination.

1.3 Vaccination of risk groups

In addition to vaccination for diseases included in the NIP, through the National Influenza Prevention Programme (NPG) influenza vaccination is offered 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 children of immigrants from high-prevalence countries. For developments with regard to 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 [2-5].

In addition to the vaccination against HBV included in the NIP, an additional vaccination programme that targets groups particularly at risk of HBV due to sexual behaviour and prostitutes is in place in the Netherlands [6].

Information on vaccination of travellers and employees at risk of work-related infections can be found on the website *www.rivm.nl/vaccinaties*.

1.4 Vaccination outside of public vaccination programmes

A number of registered vaccines in the Netherlands are available to the public outside of public programmes, at a person's own expense. Information on these can be found on *www.rivm.nl/vaccinaties*. Vaccinations registered for infants are those against gastro-enteritis caused by rotavirus infection, varicella, and meningococcal B disease (MenB). For older children and adults, influenza, MenACWY and pertussis vaccinations are available. For older people, vaccinations against herpes zoster, pneumococcal disease and pertussis are available. In addition, HPV vaccination for boys, hepatitis A vaccination for MSM, as well as hepatitis B vaccination for first and second generation migrants from countries where Hepatitis B is

endemic are available. Professional guidelines are also available on herpes zoster, maternal pertussis vaccination, pertussis vaccination for adults, HPV vaccination outside the NIP, meningococcal ACWY vaccination, meningococcal B vaccination, rotavirus vaccination, varicella zoster vaccination, pneumococcal vaccination for the elderly, and hepatitis B vaccination. A guideline for hepatitis A vaccination is currently under development.

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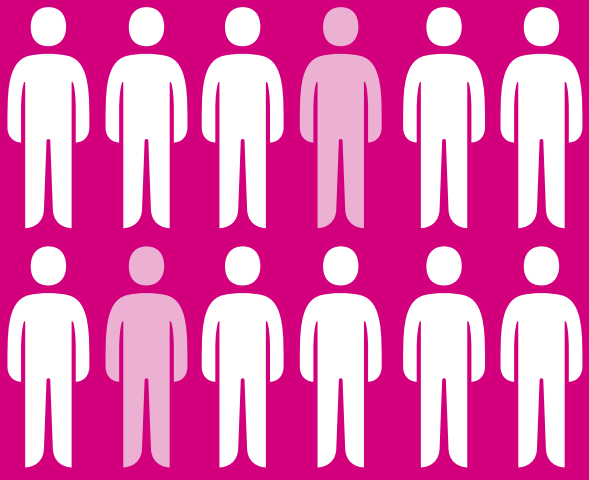
2
Vaccination coverage



E.A. van Lier

2.1 Key points

- Vaccination coverage in the Netherlands is still high but has declined slightly between 2014 and 2018. Vaccination coverage for most vaccinations has now fallen by around 2-3% in total.
- For the HPV vaccination, coverage has decreased by 15% since 2016, with a remarkable decline of 8% compared to last year. The main reasons given for not vaccinating against HPV or for having doubts are concern possible side effects of the HPV vaccine.

2.2 Tables and figures

Table 2.1 Vaccination coverage (%) per vaccine for age cohorts of newborns, toddlers, schoolchildren and adolescent girls in 2006–2018 [1]

Report year	Newborns*							
	cohort	DTaP -IPV	Hib	HBVa	PCV **	MMR	MenC	full ***
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	
2016	2013	94.2	94.9	93.8	93.8	94.8	94.6	
2017	2014	93.5	94.2	93.1	93.6	93.8	93.5	91.2
2018	**2015**	**92.6**	**93.4**	**92.2**	**92.8**	**92.9**	**92.6**	**90.2**

Table continued on next page

Report year	Toddlers*				Schoolchildren*			Adolescent girls*	
	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
2016	2010	91.5	2.1	93.7	2005	92.0	92.0	2001	61.0
2017	2011	91.1	2.1	93.2	2006	90.8	90.9	2002	53.4
2018	**2012**	**90.4**	**2.3**	**92.7**	**2007**	**90.0**	**90.1**	**2003**	**45.5**

* Vaccination coverage is assessed at the ages of two years (newborns), five years (toddlers), 10 years (schoolchildren) and 14 years (adolescent girls).
** Only for newborns born on or after 1 April 2006.
*** Key figure full participation newborns: received all NIP vaccinations at two years of age.
**** 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; only 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).
Source: Præventis

2.3 Vaccination coverage

The vaccination coverage, i.e. the proportion of newborns, toddlers and schoolchildren who receive the vaccinations within the NIP, is still high but has declined slightly in recent years (around 2-3% since 2014). For the HPV vaccination, the further decrease in the immunisation coverage of 8% compared to last year is remarkable, which now has fallen by 15% since 2016. The main reasons given for not vaccinating against HPV or for having doubts are concern possible side effects. Soon, the Health Council will issue a new advice on HPV vaccination in the Netherlands [1].

A high vaccination coverage ensures that vulnerable and (still) unvaccinated individuals are protected against diseases (group protection). A decreasing vaccination coverage increases the

likelihood of future breakouts of diseases like measles. In addition, the increased number of unvaccinated people is a missed opportunity for individual protection against NIP diseases [1]. Extrapolating current trends for HPV based on data from a previous study [2], it is estimated that a decrease in the vaccination coverage from 61% to 46% will prevent around 60 fewer cases of cervical cancer per birth cohort. This calculation is conservative, however, because (i) the incidence of cervical cancer (and therefore the proportion to be prevented) has risen in the last 10 years, and (ii) the expected benefit of vaccination is probably not limited to the vaccine types [1]. Thereby, vaccination also protects against cancers other than cervical cancer.
Data on provisional vaccination coverage indicate that the declining trend for newborns seems to be stabilising from birth cohort 2016 (the most recent report covers cohort 2015). Preliminary attendance figures for HPV for birth cohort 2004 (the most recent report covers cohort 2003) indicate that the end of the declining trend for HPV may not yet be in sight, but that it seems to be levelling off. It is important to continue to follow these developments closely in the future [1].

Research into changes in the organisational aspects of youth health care has not provided any new leads regarding possible reasons for the drop in vaccination coverage [1]. An external advisory committee on willingness to vaccinate recently recommended a change of perspective: the perspective of the citizens / parents involved should be more central. According to the committee, instead of a one-sided, supply-based approach based on biomedical knowledge about vaccination and group immunity, an interactive approach based on multidisciplinary knowledge is necessary [3].

In a number of surrounding countries, concerns are also being voiced about a decreasing vaccination coverage and an increase in vaccine hesitancy. This is a reason for making vaccination or a conversation about vaccination obligatory in some countries. The European Parliament has also put the issue on the political agenda. In the Netherlands, despite a slight downward trend, vaccination coverage with voluntary vaccination is still high, with the exception of HPV vaccination [1].

2.4 Literature

2.4.1 References

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*RIVM publication

2.4.2 Other recent RIVM publications

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3
Acceptance of vaccination

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3.1 Key points

- Attitude and trust in vaccinations is still high among those parents who vaccinate their children.
- Side-effects, doubts about the effectiveness of the HPV-vaccine, too little information, and negative stories about HPV vaccination were the most important reasons voiced by parents regarding their decision not to vaccinate their daughters against HVP.
- Adolescents and parents had a relatively positive attitude towards MenACWY vaccination.
- Among GPs and GP nurses, the need for and effectiveness of vaccination in general was high, and somewhat lower for the MenACWY and HPV vaccinations.
- Women of childbearing age are neutral/positive towards maternal pertussis vaccination; providing information had a significant positive influence on their attitude.

3.2 Monitoring acceptance NIP

3.2.1 NIP in general

With vaccination coverage falling in many countries, including the Netherlands, it is important to explore the reasons why the public is becoming less willing to vaccinate. Research into these questions can help us to develop interventions that may halt the decline in the vaccination coverage. Below, a range of research is described regarding childhood vaccinations, reasons for not vaccinating girls against HPV, how MenACWY vaccination should be organised and the development of informational material for pregnant women and an e-learning programme for midwives. The report by the external advisory committee about willingness to vaccinate was discussed in Chapter 2 "vaccination coverage".

In December 2017, parents with at least one child aged between 2-4 years were asked to complete a questionnaire about their attitude to full vaccination, partial vaccination, and no vaccination (N = 2,556 (14%)). This study was part of the four-year RIVM SPR-project “RICALTS” about ‘second-best’ communication. This project aims to answer the question: ‘If we also communicate second-best options such as later vaccination or omitting certain vaccinations, would this result in public health gain or public health loss?’ The sample included similar numbers in each cohort: 839 fully vaccinated, 737 partially vaccinated and 980 not vaccinated. As expected, parents who had their child fully vaccinated were most positive about full vaccination on a Likert-scale of 1 to 7 (1=very important, 7=not important at all) for parents who fully vaccinate, partly vaccinate and do not vaccinate their child (6.2, 3.8 and 2.4 respectively). These figures were comparable to the findings from previous years (in 2013, 2015; different samples). We also asked the parents about their attitude towards partial vaccination and no vaccination: partial vaccination parents scored 3.2, 5.3 and 3.8 respectively,

and no vaccination parents responded 2.2, 3.7 and 5.8, respectively. Reported trust in government/Public Health Institute/CVPs/vaccinations/the NIP and the information about the NIP remained high among those who vaccinate (5.4 on a scale of 1 to 7), and somewhat lower among those who partly vaccinate or do not vaccinate at all (4.0 and 3.6 respectively). Here, again, these results were similar to previous years. We also asked the parents where they looked for information about vaccination. The top 6 sources of information were: 1. internet (75%), 2. PHI (65%), 3. CVPs (58%), 4. family (43%), 5. the website of a Dutch association critical of vaccination (NVKP) (42%), and 6. friends. There were some differences between the groups: for parents who fully vaccinate their children, CVPs were in second place; the NVKP was in fourth place among parents who partially vaccinate their child and third place among parents who do not vaccinate their child; while the NVKP was not in top 6 among parents who fully vaccinate their child. Parents who do not vaccinate (5.5 on a scale of 1 to 7) or those who partially vaccinate their child (6.0) estimated their own knowledge about the NIP as better than the parents who do vaccinate their child did (5.0). However, when asked about factual knowledge, the parents who vaccinate had more knowledge (7 of 9) than those who partially vaccinate (6 of 9) or those who do not (4 of 9). We also asked them about their beliefs in relation to certain items of knowledge. By presenting statements such as "I believe vaccinations do not help to prevent infectious diseases in the Netherlands" and "Due to vaccinations, most of the infectious diseases that we vaccinate against have been practically eradicated". We found that those parents who vaccinate partially and those who do not vaccinate their child at all answered these questions incorrectly based on their beliefs. It is therefore important that when talking to parents about these facts, their beliefs are also addressed.

3.2.2 Reasons for parents' decision to vaccinate their daughters against HPV

In March/April 2018, a survey was carried out among parents of girls who were invited for a HPV vaccination in 2016 ((birth cohort 2003; N = 554 (7%)) in order to gain more insight into their decisions regarding vaccination. Of this group, 29% of the girls were not vaccinated, 8% had one vaccination, and 62% had two HPV vaccinations. The most important reasons (open question) why they were not vaccinated against HPV were: concerns about side-effects of HPV vaccine (40%); doubts about effectiveness of the HPV vaccine (12%); too little information about HPV vaccination (10%); and negative stories about HPV vaccination (10%). When asked closed questions, the respondents again reported being most worried about side-effects (65%), doubts about the effectiveness of the HPV vaccine against cervical cancer (37%), and negative stories about the HPV vaccination in the media (35%). The most important reasons given in favour of vaccination were: prevention (protection) (60%); reducing the risk of an HPV infection and/or contracting cervical cancer (17%); trust (in healthcare professionals, government, science) (5%); and own experience (smear test, cervical cancer, environment) (5%). When asked closed questions, the parents reported that cervical cancer is a serious disease (58%), trust in the effectiveness of the HPV vaccine against cervical cancer (50%), that the benefits of vaccination outweigh possible side effects (34%), and that vaccination is the best form of protection (28%). About 38% of parents/guardians (31% of those who vaccinate and 52% of those who do not vaccinate) reported that they or their daughter had doubts about the HPV vaccination. The most important reasons for those doubts were concerns about

side-effects of the HPV vaccine (37%), contradictory/negative messaging about the HPV vaccination (20%), lack of information about the HPV vaccination (15%), and the difficulty of assessing the risks (9%). Among the participants, 27% reported that something should change in the way that the HPV vaccination is offered: information about the HPV vaccination (68%), the organisation of the HPV vaccination (19%), and more research (7%). The final decision on having the HPV vaccination or not was, in most cases (61%), taken by both the parents and the daughter together.

3.2.3 Attitude and organisation MenACWY vaccination for adolescents

3.2.3.1 Adolescents and parents

IIn November 2017, a questionnaire was sent to adolescents and parents to ask what they thought about MenACWY vaccination for adolescents and about how this should be organised. In total, 115 adolescents (92% reported participating in the NIP) and 106 parents (of which 57 were adolescent-parent dyads; 89% reported vaccinating their child according to NIP guidelines) completed the questionnaire. Among adolescents, 74% reported a positive attitude (5-7 on a scale of 1 to 7) towards vaccination in general and 77% for vaccination against meningococcal disease; among parents, this was 88% and 73%, respectively. Among adolescents, 61% intended to be vaccinated against meningococcal disease; this was 70% among the parents. Among adolescents, 83% reported the view that meningococcal disease is a serious disease, and 50% reported that they thought they would have a high chance of contracting meningococcal disease; parents scored 91% and 24%, respectively. Among adolescents, 96% reported that they would discuss their decision regarding vaccination with their parents, 20% with friends, 19% with their GP, 18% with class mates, 9% with their teacher, 8% with child vaccine providers, and 3% with nobody. Regarding the information needed, most of the adolescents (79%) noted that they would like to receive information about the risk of contracting meningococcal disease, and about the effectiveness of vaccination (63%), while among parents most (89%) would like to receive information about the risk of side-effects. Adolescents would like to receive information from their GP (57%) and from school (50%); most parents reported the PHI (70%) as their favoured source of information. Both adolescents and parents would like to receive information by means of a letter and brochure (54% and 80%, respectively). They would like to receive the vaccination from their GP (57% and 58% respectively) and would like a parent to be present when the vaccine is administered (86% and 88%, respectively). About half the participants (47% and 53% for adolescents and parents respectively) would like to receive the vaccination in group vaccinations; 55% of the parents (64% for adolescents) would prefer an individual consultation. Moreover, about half the participants (53% and 50% for adolescents and parents, respectively) would like to have a meeting (face to face (80%)) with a professional before the vaccination is administered (correlated with wanting an individual consultation for parents only). Among girls and parents with a daughter, 63% intended to have vaccines against both HPV and meningococcal disease; and adolescents (87%) and parents (95%) would like to receive these simultaneously. Among adolescents and parents, intention to have only the MenACWY vaccination was 19% and 24% respectively, while intention to have neither vaccine was 18% and 14%, and intention to have the HPV vaccine only was 0%.

3.2.3.2 *General Practitioners*

In April 2018, a survey was carried out among GPs visiting the GP Fair (huisartsenbeurs) (N=112) in order to discover more about their attitudes regarding the MenACWY vaccination among adolescents. Of the 112 participants, 79% were female with a mean age of 43 years (range 20-70 years). Regarding their profession, 58% were GPs, 21% GP nurses (doktersassistent), and 21% reported another health profession. Among the participants, 94% reported that vaccination in general was needed (4 5 on a likert scale 1-5), 67% reported that the MenACWY vaccination was needed among adolescents, and 76% reported that the HPV vaccination was needed among adolescent girls. With regard to effectiveness, 94% of the participants reported that vaccination in general is effective (4-5 on a Likert scale 1-5), 85% stated that the MenACWY vaccination was effective, and 73% reported that the HPV vaccination was effective. About 12% of the participants reported having received questions about meningococcal vaccination and/or disease. Participants were asked about their role in MenACWY vaccination among adolescents: 56% reported answering questions; 43% providing information; 37% providing advice; 33% educating; 21% referring; 15% vaccinating; 9% no task; and 1% other. Lastly, participants were asked how they would prefer to be informed about the MenACWY vaccination: 46% reported via the RIVM website; 43% E-learning; 33% guidelines; 20% factsheet; 10% workshop; 7% decision aid; 5% Youtube podcast; 4% no information needed; and 3% other.

3.2.4 Attitude and need for information about maternal pertussis vaccination among women

In February and March 2018, a survey was carried out in the north of the Netherlands among women of childbearing age regarding their attitude towards the effectiveness and safety of the maternal pertussis vaccination (MPV), and about their need for information. In addition, they studied whether the attitude of women could be influenced by providing information about pertussis and the pertussis vaccine. The results showed that the average attitude towards MPV was neutral-positive. Furthermore, the provision of information had a significant positive effect on the attitude of women, especially when they had not previously been informed properly. Of the participants in the survey, 75% had not been informed about MPV, and 91% wanted to receive information about MPV. They stated that they would prefer to be informed at the start of their pregnancy, and to receive a brochure from the person providing care during their pregnancy or from the RIVM. In addition to this survey, a brochure about MPV was developed for pregnant women and an e-learning programme for midwives.

3.3 International developments

3.3.1 Interventions to increase HPV vaccination coverage

As in the Netherlands, both Ireland and Denmark have seen a large decline in HPV vaccination coverage. Denmark launched a large "Stop HPV campaign" (consisting of distributing posters and leaflets in GP offices; factsheets for professionals; a new website with personal stories and an active Facebook page; collaboration with the press and journalists), which, after nine months, resulted in an increase in confidence in the HPV vaccination and an increase in uptake. *(http://www.who.int/features/2018/hpv-vaccination-denmark/en/).* In Ireland, an HPV vaccination

alliance, training programme for health professionals including e-learning, revised printed and online materials, online videos, a media campaign featuring vaccinated girls, and offering unvaccinated girls another opportunity to be vaccinated, also resulted in an increase in the first dose uptake. *(https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(18)30854-7.pdf).*

3.3.2 Communication

Studies show that simply correcting myths about vaccines may not be effective, and that they may even backfire as repeating myths can inadvertently reinforce them. First, the myth has to be explained: where does it come from? Who is repeating the myth? Which techniques are used by vaccine deniers (see below)? In this way, a positive association with vaccination is reinforced and an alternative explanation for the myth is provided. *(http://www.who.int/bulletin/volumes/95/10/17-021017.pdf; http://www.euro.who.int/__data/assets/pdf_file/0005/315761/Best-practice-guidance-respond-vocal-vaccine-deniers-public.pdf).* Most hesitant parents do not challenge the scientific evidence, but the messages of vaccine deniers make them feel doubtful and fearful. Public health authorities need to build confidence and educate the public continuously, so that people are better prepared to make vaccination decisions when they are faced with them. Five techniques are mentioned that vaccine deniers use to make their claims sound plausible: impossible expectations; false logic; claims of technical expertise; the argument that governments promote vaccination because of undue influence from the pharmaceutical industry; and selectivity - when arguments are built based on isolated scientific papers. *(http://www.who.int/bulletin/volumes/95/10/17-021017.pdf)*

3.3.3 Recent WHO-EURO and ECDC documents

Best practice guidance on how to respond to vocal vaccine deniers in public. The most important rules are: the general public is your target audience, not the vocal vaccine denier; and aim to unmask the techniques used by the vocal vaccine denier and to correct the content, with the aim of making the public more resilient to anti-vaccine misinformation and stories. This supports vaccine-hesitaters in their acceptance of vaccines.
http://www.euro.who.int/__data/assets/pdf_file/0005/315761/Best-practice-guidance-respond-vocal-vaccine-deniers-public.pdf

The WHO Report "Vaccination and Trust" *(http://www.euro.who.int/en/health-topics/disease-prevention/vaccines-and-immunization/publications/2017/vaccination-and-trust-2017)* presents the scientific evidence behind the WHO's recommendations on building and restoring confidence in vaccines and vaccination, both through ongoing work and during crises. The evidence draws on a vast body of laboratory research and fieldwork in the fields of psychology and communication. It examines how people make decisions about vaccination and why some people are hesitant about vaccination. It also looks at the factors that drive a crisis, considers how building trust, listening to and understanding people, building relationships, communicating risks and shaping messages for specific audiences can help to mitigate crises. This background document is part of the Vaccination and trust library *(http://www.euro.who.int/en/health-topics/disease-prevention/vaccines-and-immunization/publications/vaccination-and-trust)*, which includes a series of support documents with practical guidance for specific situations.

The ECDC's technical report "Catalogue of interventions addressing vaccine hesitancy" *(https://ecdc.europa.eu/en/publications-data/catalogue-interventions-addressing-vaccine-hesitancy)* provides tools and information resources to support EU/EEA countries in addressing the challenging issue of vaccine hesitancy. The catalogue provides examples of practices that can serve as a resource for other countries. The project was developed in the context of the ECDC's support for EU/EEA Member States in preventing and controlling vaccine-preventable diseases, including effective communication to promote immunisation.

Questions and Answers about HPV – Information for health professionals to help them to answer frequently asked questions by parents and adolescents includes Q&As about the introduction of the HPV vaccine, the HPV vaccine, and quality, safety and side effects. *(http://www.euro.who.int/__data/assets/pdf_file/0011/356843/QA_HPV_Health-professionals_EN.pdf)*

4
Burden of disease

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4.1 Key points

- The estimated disease burden caused by (partly) vaccine preventable diseases expressed in Disability Adjusted Life Years (DALY) for the year 2017 was highest for invasive pneumococcal disease (9,800 DALY/year), pertussis (2,000 DALY/year), invasive meningococcal disease (1,100 DALY/year), and rotavirus infection (1,100 DALY/year).
- In a separate analysis, the average annual disease burden for HPV in the 2011–2014 period was estimated at 13,800 DALY (76% among women), higher than the burden of any of the diseases mentioned above.
- Compared with the estimated burden in 2016, the burden in 2017 was relatively high for invasive meningococcal disease, hepatitis A, rotavirus infection, and pertussis.

4.2 Tables and figures

Table 4.1 Estimated annual disease burden in DALY in 2013–2017, and DALY per 100 infections in 2017 in the Netherlands (with 95% uncertainty intervals) [1, 2]

Disease	DALY (95% uncertainty interval)					DALY/ 100 infections
	2013	2014	2015	2016	2017	
Diphtheria	0 (0–0)	1 (1–2)	4 (3–5)	2 (2–3)	2 (2–2)	95 (77–110)
Hepatitis A virus infection	59 (36–98)	57 (35–94)	43 (27–72)	44 (27–73)	200 (120–340)	11 (8–15)
Hepatitis B virus infection (acute)	400 (370–420)	250 (230–260)	100 (95–110)	180 (170–200)	150 (140–160)	26 (24–28)
Human papillomavirus infection[a]						
• *Females*	10,000 (9,300–10,700)	10,800 (10,100–11,600)				n.a.
• *Males*	3,700 (3,000–4,500)	3,700 (3,000–4,500)				n.a.
Invasive *H. influenzae* disease	610 (580–650)	690 (650–730)	840 (800–890)	860 (800–910)	980[b] (930–1,000)	390 (370–410)
Invasive meningococcal disease	780 (630–950)	590 (460–730)	560 (440–700)	870 (720–1,000)	1,100[c] (980–1,300)	550 (510–600)
Invasive pneumococcal disease	10,800 (10,200–11,400)	9,100 (8,500–9,600)	10,900 (10,200–11,500)	9,800 (9,200–10,500)	9,800[d] (9,200–10,400)	360 (330–380)
Measles[e]	580 (510–650)	28 (26–31)	1.1 (0.9–1.2)	1.1 (0.9–1.3)	3 (2–3)	2 (1–2)
Mumps	2 (1–2)	0.3 (0.3–0.3)	0.7 (0.6–0.7)	0.5 (0.5–0.6)	0.4 (0.3–0.4)	0.4 (0.4–0.4)
Pertussis	1,400 (1,300–1,500)	3,600 (3,300–3,900)	2,700 (2,500–2,900)	1,500 (1,400–1,600)	2,000 (1,900–2,200)	1 (1–1)
Poliomyelitis	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	n.a.
Rabies	35 (35–35)	49 (49–49)	0 (0–0)	0 (0–0)	0 (0–0)	n.a.
Rotavirus infection	1,400 (590–2,800)	600 (250–1,200)	1,300 (520–2,500)	670 (280–1,300)	1,100 (440–2,200)	0.5 (0.3–0.9)
Rubella	4 (3–5)	210 (170–260)	0.06 (0.04–0.08)	0 (0–0)	0 (0–0)	n.a.
Tetanus	6 (5–7)	0 (0–0)	9 (7–10)	2 (2–2)	0.6 (0.5–0.8)	53 (51–55)

DALY= disability-adjusted life years

n.a.= not applicable; no cases occurring in 2017 or unknown number of infections (HPV)

a Annual burden estimates not available for 2015–2017. To estimate the burden, the numbers of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV were used.

b Proportion caused by the vaccine preventable type b in 2017: 29%.

c Proportion caused by the vaccine preventable type C in 2017: 3%; proportion caused by type B in 2017: 54%; proportion caused by type W in 2017: 36%.

d Proportion caused by the vaccine preventable types 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F in 2017: 11%.

e Note that the burden estimates are considerably lower than reported previously due to an update of the measles case-fatality rate.

Sources: OSIRIS, NRLBM, sentinel laboratory surveillance, national cancer registry, PALGA, NIVEL-LINH

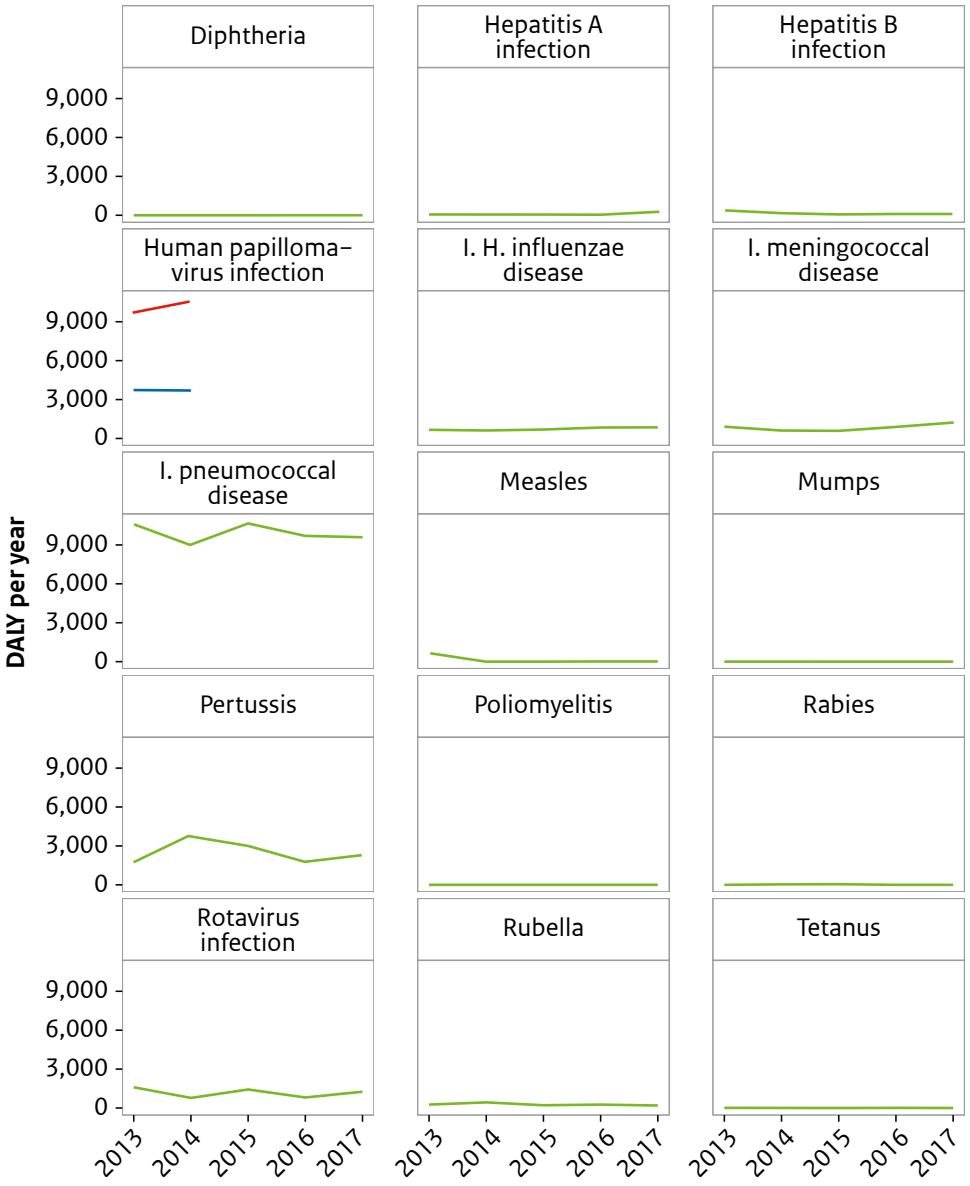


Figure 4.1 Estimated annual disease burden in DALY in 20132017 in the Netherlands [1, 2]

1. Vaccination against rabies, hepatitis A and rotavirus infection is not included in the NIP.

2. For the three invasive diseases, a vaccine was only available against certain serotypes: *Haemophilus influenzae* serotype b (Hib), meningococcal C and pneumococcal serotype 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F. For HPV infection, a vaccine was only available against two types: HPV 16 and 18.

3. For HPV, the burden is based on the number of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV. The red line shows the burden for females, the blue line shows the burden for males.

4. Note that the burden estimates for measles are considerably lower than reported previously due to an update of the measles case-fatality rate.

Sources: OSIRIS, NRLBM, sentinel laboratory surveillance, national cancer registry, PALGA, NIVEL-LINH

4.3 Burden of disease

In this section we present an update of the disease burden expressed in disability-adjusted life years (DALY) of vaccine-preventable diseases in the period 2013–2017. We present the same estimates published in the 'State of infectious diseases in the Netherlands, 2017', in which more detailed information on the parameters used can be found [1]. Note that the burden estimates for measles are considerably lower than reported previously due to an update of the measles case-fatality rate. Estimates for human papillomavirus (HPV) infection were derived from a previous separate analysis [2]. Note that the calculation method used for HPV is not fully comparable to other diseases: a different period (2011–2014) and life table (Dutch life expectancy 2014) were used and, instead of using the number of incident infections (which are unknown), the numbers of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV were used. All DALY estimates were rounded: to three significant digits for numbers ≥10,000, to two significant digits for numbers between 10 and 10,000 and to one significant digit for numbers <10.

Table 4.1 shows the estimated DALY per year in the period 2013–2017 and the DALY per 100 infections in 2017 (a measure of the disease burden at individual patient level) in the Netherlands, with 95% uncertainty intervals. For poliomyelitis, rabies and rubella, the estimated disease burden in 2017 was zero because no cases were reported. For mumps, tetanus, diphtheria, and measles, the disease burden in 2017 was estimated to be very low, while the highest burden was estimated for HPV infection (based on the burden in 2013–2014 instead of 2017), followed by invasive pneumococcal disease, pertussis, invasive meningococcal disease and rotavirus infection.

The influence of outbreaks on the disease burden is apparent in Table 4.1 and Figure 4.1. The 2013/14 measles outbreak is visible, as is that of rubella in 2014, and hepatitis A in 2017. The incidence of pertussis and rotavirus infection is known to surge every few years, which is also visible in Table 4.1. For both diseases, the incidence in 2017 was relatively high. For invasive meningococcal disease, the burden in 2017 was relatively high because of the continuing rise in the number of patients caused by serogroup W.

It must be noted that the total disease burden for pneumococcal disease, meningococcal disease, and *Haemophilus influenzae* disease is higher than presented here because we limited our analyses to invasive disease. The disease burden related to hepatitis B virus infection has also been underestimated. Our analyses only reflect the (future) burden of new cases of hepatitis B virus infection in the period 2013–2017, which means that the disease burden of (chronic) hepatitis B cases infected prior to this period is not included.

4.4 Literature

4.4.1 References

1.* de Gier B, Mooij S, Hahné SJM. State of Infectious Diseases in the Netherlands, 2017. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2018. RIVM report 2018-0032.

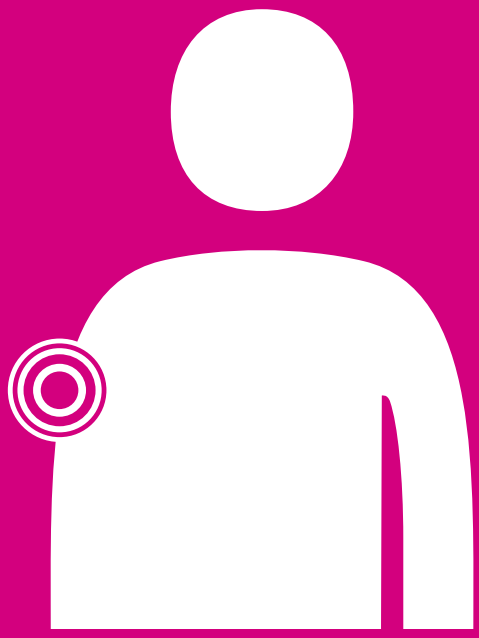
2.* McDonald SA, Qendri V, Berkhof J, de Melker HE, Bogaards JA. Disease burden of human papillomavirus infection in the Netherlands, 1989-2014: the gap between females and males is diminishing. Cancer Causes Control. 2017;28(3):203-14.

*RIVM publication

4.4.2 Other recent RIVM publications

1. Cassini A, Colzani E, Pini A, Mangen MJ, Plass D, McDonald SA, et al. Impact of infectious diseases on population health using incidence-based disability-adjusted life years (DALYs): results from the Burden of Communicable Diseases in Europe study, European Union and European Economic Area countries, 2009 to 2013. Euro Surveill. 2018;23(16):pii=17-00454.

5
Adverse events



J.M. Kemmeren

5.1 Key points

- In 2017, Lareb received 1,383 reports of a total of 5,423 adverse events following immunisation (AEFI). Compared to 2016, the number of reports declined by 6.7%, while the number of reported AEFIs increased by 48%. This increase is due to a change in recording local reactions.
- No signal emerged to indicate that vaccines used in the NIP were unsafe.

5.2 Tables and figures

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

Vaccines	Total 2016	Total 2017	2m	3m	4m	11m	14m	4yr	9yr	12-13yr	Other/ Unknown
Infanrix hexa® + Synflorix®	387	**456**	208		86	148					14
Infanrix hexa®	88	**109**	5	73	6	4					21
Synflorix®	7	**11**	3		2	2					4
MMRvaxPro® + NeisVac-C®	163	**191**					189				2
MMRvaxPro®	10	**19**					10		2		7
NeisVac-C®	5	**3**					1				2
Infanrix-IPV®	575	**219**						217			2
Boostrix® Polio		**172**						170			2
MMRvaxPro® + DTP-NVI	75	**19**							19		
Revaxis® + MMRvaxPro®	8	**83**							83		
DTP-NVI	5										
Revaxis		**6**							2		4
Cervarix®	146	**85**								77	8
Other	14	**10**									10
Total 2017		**1,383**	216	73	94	154	200	387	106	77	76
Total 2016	1,483		174	60	95	126	171	572	84	146	55
Total 2015	1,494		173	69	87	142	208	422	88	257	48
Total 2014	982		148	64	74	101	139	274	108	59	15
Total 2013	1,212		217	118	75	118	133	335	92	82	42
Total 2012	1,387		250	154	110	103	138	423	52	104	53
Total 2011	1,103		212	154	86	105	129	280	51	51	35

Source: Lareb [1]

Table 5.2 Reported severe adverse events per vaccination moment

	2m	3m	4m	11m	14m	4yr	9yr	12yr	Other/ unknown	Total
Rash, eczema	15	6	11	19	94	17	15		11	188
Respiratory symptoms, decreased consciousness										99
Collapse, (pre)syncope	5	1	1	3	3	14	12	7		46
Apnoea, dyspnoea, irregular breathing	3	2	2	5	6	3	1	2	2	26
Hypotonic-hyporesponsive episode (HHE)	11		1	2	1					15
Breath holding spells	2	3	2		2				1	10
Apparent life threatening event (ALTE)	2									2
Extensive swelling of vaccinated limb (ELS)	2	2	2	4		59	1	1	4	75
Convulsions, epilepsy										52
(febrile) Convulsions, seizures	4	1	6	9	14	3	1		3	41
(febrile) Delirium					1	1	2			4
Epilepsy, status epilepticus		1		1	2				3	4
Ataxi, spasm, tic					1		1		1	3
Fever >40.5 °Celsius	5	3	2	9	19	7	2	1	1	49
Allergic reaction, anaphylaxis	1	1	1	7	8	7	4	4		33
(persistent) Crying	4	4	1	3	5	1			2	20
Skin discolouration	6	1	4		1	1				13
Abscess	1	1	2	3						7
Immune mediated disorders										5
Diabetes mellitus							1	1		2
Acute haemorrhagic oedema of infancy				1						1
Immune thrombocytopenic purpura (ITP)					1					1
Kawasaki's disease	1									1
Dehydration	1				1			1		3
Death	1				1					2
Encephalitis, meningitis	1					1				2

	2m	3m	4m	11m	14m	4yr	9yr	12yr	Other/ unknown	Total
Postural orthostatic tachycardia syndrome (POTS)									1	1
Vaccine failure										0
Chronic fatigue										0
Venous thrombosis										0
Chronic arthritis										0
Complex regional pain syndrome (CRPS)										0

Source: Lareb (1)

5.3 Spontaneous reporting system

5.3.1 Reports

The enhanced passive surveillance system managed by the National Centre for Pharmacovigilance Lareb receives reports of AEFI for all vaccines included in the NIP. In 2017, Lareb received 1383 reports with a total of 5423 AEFI (Table 5.1) [2]. Compared to 2016, the number of reports declined by 6.7% (1483 in 2016), while the number of reported AEFIs increased by 48% (3665 in 2016). From January 2017, both redness and swelling have been recorded separately. As a result, the number of suspected adverse reactions after vaccination per report is higher in this report than in previous years. The number of reports has not increased. Most reported AEFIs were crying (n=234), fever (n=608) and injection site reactions (erythema n= 476, swelling n= 440; pain n=393; warmth n=388). Of the reports, 92 (6.7%) were classified as serious.

Compared to 2016, the number of reports increased in 2017 for most of the vaccination moments (see Table 5.1). After a decline in number of reports in the period 2014-2016 for the vaccinations at the age of 2 months, this number is back to the level before 2014. The number of reports after vaccinations at the age of 3 months has dropped since 2013. This may be due to the change of a 3-dose to a 2-dose schedule for PCV10 in December 2013. For infants aged 11 months and 14 months, the number of reports has increased since 2015,an explanation for this increase is lacking. After administration of DTP-IPV at the age of 4 years, a lower number of reports (n=387) were received compared to 2016 (n= 572) and 2015 (n=422). In 2017, another vaccine with a low-dose antigen content was introduced for this age group, and it appears that the number of reports of Extensive Limb Swelling is now decreasing. The RIVM and Lareb will monitor this effect. Since 2013, an increase in reports after the MMR and dT-IPV vaccination was seen in children aged 9 years. A possible explanation may be the change from wP- to aP-containing vaccines in the primary series in 2005, although this is not confirmed by a questionnaire based study about the reactogenicity of dT-IPV vaccination at 9 years of age in children primed in infancy with an aP-vaccine compared to children primed with a wP-vaccine (Kemmeren et al, unpublished results). The number of notifications received after

administration of the HPV vaccine declined from 257 in 2015, 146 in 2016 to 77 in 2017. Overall, there is no indication that vaccines used in the NIP are unsafe.

Table 5.2 summarises severe adverse events per vaccination moment reported to Lareb. These events are included because of their severity and their known or perceived relation with vaccination. In general, the spectrum of reported AEFI is mostly in line with previous years. Only, as earlier mentioned, a decline in reports of extensive limb swelling (n=59) among 4-years-olds was noticed (76 in 2014 and 110 in 2015). The increase of ELS after dT-IPV vaccination in 9-years-olds noted in earlier years was not seen in 2017.
No reports of postural orthostatic tachycardia syndrome (POTS) and chronic fatigue syndrome (CFS) after HPV vaccination were received. Fatigue after HPV vaccination was reported 30 times, with long-term complaints such as fatigue, fainting and headache notified in one report. However, this case did not meet the case-definition of CFS.
Two cases of death were reported, one following vaccination at 2 months of age and one following vaccination at 14 months of age. In one case, death was unlikely to have been caused by the vaccination. For the other case, no additional information was available.

5.3.2 Signals

Between January 1, 2012 - July 5, 2017 the Pharmacovigilance Centre Lareb received 35 reports of one or more injection site abscesses after administration of Infanrix hexa® and or Synflorix® in infants. In most reports of injection site abscesses with a known vaccine, the abscess occurred at the injection site of Infanrix hexa® (79%). Only once was an abscess reported occurring at the injection site of Synflorix® (3%); abscess occurring at both injection sites was reported 5 times (17%). The findings of Lareb over the period January 2012 - July 2017 correspond to the findings of the RIVM over the period 1994-2010. However, the RIVM found over the period 1994-2010 that there was only a slight variation in reporting rate between the four different vaccination moments in infants. In the case series of Lareb, the differences between the four vaccinations moment were more pronounced. Most injection site abscesses were observed after the 3rd or 4th administration at the injection site of Infanrix hexa®, compared to Synflorix. Lareb recommends that health care professionals and patients should be informed about this potential adverse reaction..

5.4 International developments

5.4.1 Vaccines targeting diseases included in the current NIP

5.4.1.1 MMR

In a systematic review about pain after MMR vaccination, it was shown that Priorix caused significantly less immediate pain compared with M-M-R II [3]. Tosun found that in the short term, a single component measles vaccine was safe in previously MMR vaccinated children [4]. Furthermore, MMR vaccine was safe in multiple myeloma patients [5] and in patients using interleukin (IL)-1 or IL-6 blocking agents [6] although in this case series of seventeen patients, one patient developed pneumonia after an MMR booster vaccination. A non-inferiority, clinical study showed that the safety profile of a disposable-syringe jet injector in toddlers was similar

to needle-syringe except for injection site reactions which were higher with the disposable-syringe jet injector. The vaccine was well-tolerated [7].

5.4.1.2 *Pneumococcal vaccine*

An ecologic register-based study found no increases in the incidence of adverse events after PCV10 introduction, except for urticarial rash (IRR 1.54; 95% CI 1.42-1.67)[8]. Other studies showed the safety of PCV13 in infants, in healthy children aged 6-17 years, and in children aged between 1-18 years diagnosed with cancer [9-11]. A good safety profile of a booster dose of PCV13 was also shown in children primed with PHiD-CV or PCV13, which suggests that PCV13 can be used as a booster in the context of mixed schedules [12]. Failure of PCV7 and PCV13 vaccines is rare. However, compared to PCV7 serotypes, the additional PCV13 serotypes are more likely to cause bacteremic lower respiratory tract infection and empyema in healthy vaccinated children [13]. Investigational PHiD-CV/dPly/PhtD formulations were also well-tolerated in healthy infants, in children aged 2-17 years with asplenia of splenic dysfunction or co-administrated with other childhood vaccines [14-16]. The safety of PCV13 was also shown when administered to adults [17]. However, the PCV13 carrier protein CRM197 may be potentially associated with the late onset of injection-site reaction, although it does not affect the favourable risk-benefit profile of PCV13 [18]. PCV15 also displayed an acceptable safety profile in adults aged over 50 [19]. For PPV23 in adults, no safety issues have been published [20-23]. All dose levels of a novel vaccine candidate PnuBioVax are considered safe and well tolerated in adults aged 18 – 40 [24].

5.4.1.3 *Meningococcal ACWY*

No safety issues have been published in the past year for MenACWY-TT vaccination in healthy children [25-27] as well as in children and adolescents with impaired splenic activity [27]. Furthermore, no safety concerns were identified when MenACWY-TT was co-administrated with routine childhood vaccines [28] or with Tdap and 2vHPV vaccines in adolescents [29]. A review concluded that this vaccine can be co-administrated with other routine vaccines without adversely affecting the safety profile of either vaccine [30]. Similar results were found following MenACWY-CRM vaccination [31] and MenACWY-D [32], even in adolescents with a kidney transplant [33] or HIV-infected children and adolescents [34]. A booster dose of Meningococcal C vaccination in HIV-infected children and adolescents was also safe [35].

5.4.1.3 *DTaP-IPV-HBV-Hib*

Three studies demonstrated the safety of DTPa-HBV-IPV/Hib vaccine in infants, dTap-IPV when co-administrated with MMRV to children 3-4 years old, and Tdap administrated after previous Td of Tdap vaccination in young adults [36-38]). Four studies showed the safety of a fully liquid hexavalent vaccine DTaP-IPV-HepB-PRP-T vaccine in infants [39-42]. Furthermore, no difference in reactogenicity between infant boys and girls was found after DTaP-IPV-HBV-Hib vaccination [43]. PRP-CRM197 Hib vaccine was generally well tolerated in children when administered by intramuscular injection in a three-dose primary series and as a booster with concomitant routine vaccines [44].

Two studies observed an association between maternal Tdap vaccination and maternal chorioamnionitis (RR 1.23; 95% CI 1.17-1.28 and RR 1.11; 95% CI 1.07-1.15), although no

increased risk for clinically significant infant outcomes associated with maternal chorioamnionitis was found, and the relative increases corresponded to low absolute risk increases [45, 46]. Similar conclusions were drawn for the small increased relative risk of prenatal Tdap immunisation and postpartum haemorrhage (RR= 1.23; 95% CI 1.18-1.28) [46]. Despite these findings, the Committee on Obstetric Practice, Immunisation and Emerging Infections Expert Work Group concluded that there is no evidence of adverse foetal effects from vaccinating pregnant women with an inactivated virus or bacterial vaccine of toxoid, and a growing body of robust data demonstrate the safety of such use [47]. This conclusion is confirmed by a review on this topic [48].

5.4.1.5 HPV

Lin et al demonstrated the safety of the 2vHPV vaccine [49], although a meta-analyses of 24 controlled studies showed a significantly higher incidence of any solicited local symptom in the pooled 2vHPV and 4vHPV vaccine group compared to the placebo group (overall RR: 1.20; 95%CI 1.13-1.27). No difference was reported between types of HPV vaccine (pooled RR for 2vHPV: 1.25; 95%CI 1.09-1.43, pooled RR for 4vHPV 1.16; 95%CI 1.11-1.20) [50]. Two studies mentioned that subjects were discontinued due to serious injection-site symptom. In one study, one subject (<0.1%) in the placebo group discontinued due to hypersensitivity. In another study, five subjects (0.3%) in 4vHPV group withdrew due to solicited local symptoms. In others, adverse reactions were transient.

In two reviews by Martinez-Lavin, several safety concerns were raised, including serious systemic adverse events and deaths after 2vHPV vaccination [51, 52], although the integrity of the author and the quality of previous studies have been questioned [53-55]. The same applies for current reviews.

Trials about the safety of 9vHPV vaccination show that this vaccine is well tolerated in young men and women [56-59]. This is confirmed by a meta-analysis of three clinical trials assessing adverse effects on women randomly vaccinated with 9vHPV or 4vHPV [60]. One review also demonstrates an acceptable safety profile of all HPV vaccines, although injection-site reactions were slightly more common for 9vHPV vaccine than for 4vHPV vaccine [61]. In Japan, a large-scale survey was conducted to investigate any potential association between the HPV vaccines and reported symptoms [62]. Results from this study suggest no causal association between HPV vaccines and 24 reported symptoms.

5.4.1.5.1 POTS/CRPS/CFS

New studies were published assessing the association between POTS/CRPS/CFS after HPV vaccination. A case report described a young woman who developed POTS after vaccination with 2vHPV vaccine [63].

A Japanese study suggested that HPV vaccination (pooled result for 2vHPV and 4vHPV vaccination) is related to the transiently high prevalence of CRPS and autonomic and cognitive dysfunction in the vaccinated patients [64]. However, this study was biased since it examined only patients who had self-described symptoms up to two years after HPV vaccination, was not a random sample of the population, and did not contain a proper control group. A US study (with unknown vaccine type) and three reviews did not find any indications of increased risk of CRPS or CFS/ME following HPV vaccination [61, 65-68]. The RIVM investigated a

possible association between HPV-vaccination and long-term fatigue. Differences between pre- and post-vaccination incidences for CFS in a cohort of 69,429 12-16 year-old girls were not statistically significant (3.6; 95%CI 0.5-25.7/10,000 PY and 0.9; 95% CI 0.4-2.1, respectively). Self-controlled-case-series analyses with a high-risk period of 12 months after each dose in 16 consenting vaccinated cases resulted in an age-adjusted RR of 0.62 (95%CI 0.07-5.49). So, although the number of cases in the self-controlled-case-series analyses was low, no evidence was found for an increased risk of fatigue syndromes following HPV-vaccination (see section 7.4.4.8)([69]. Overall, the GACVS concluded that there is no evidence to suggest a causal association between HPV vaccine and CRPS, POTS or the diverse symptoms that include pain and motor dysfunction [70].
There is an ongoing discussion about the possible maladministration by EMA in the handling of the referral procedure on HPV vaccines. In 2016, the Nordic Cochrane Centre complained to the EU Ombudsman about how the EMA carried out a referral procedure, and about the lack of transparency, openness and impartiality related to HPV vaccines [71]. In June 2017, the Ombudsman concluded that there was no maladministration by the EMA in the handling of the referral procedure on HPV vaccines [72]. The Nordic Cochrane Centre criticised this conclusion. Their main issue was about the substandard way the EMA evaluates science, which may have consequences for public health [73]. Although they acknowledge that it is not the Ombudsman's task to take a view on science, they are concerned that there is no public safeguard against poor conduct by EMA.

5.4.1.5.2 Guillaine-Barré syndrome (GBS)
In a cohort study in France, an apparently increased risk of GBS after HPV vaccination was detected [74], with 93% being vaccinated with 4vHPV and 7% with 2vHPV vaccine. However, because of the extremely small numbers of GBS patients (1-2 per 100,000 individual increase in the risk of GBS in vaccinated groups), it is possible that random chance caused the observation. In addition, this finding was not confirmed by a study in Canada, in which no signal of increase GBS hospitalisation incidence in a 4vHPV-vaccine targeted group was detected in a hospitalisation database [75]. In addition, no association between 4vHPV vaccine and GBS was identified from VAERS and VSD-data [70].

5.4.1.5.3 Other auto-immune diseases
Several studies assessed the risk of autoimmune and/or neurological diseases associated with HPV vaccination. In a cohort study with Danish and Swedish data, incidence rate ratios of 45 preselected serious chronic diseases were compared in 4vHPV-vaccinated and unvaccinated adult women. After taking multiple testing into account and conducting self-controlled case series analyses, coeliac disease was the only remaining association [76]. According to the authors, unmasking of conditions at vaccination visits is a plausible explanation for this finding, since coeliac disease is underdiagnosed in Scandinavian populations.
Other studies provide reassuring results regarding the risk of auto-immune and/or neurological diseases after 2vHPV and/or 4vHPV vaccination [74, 76-81]. Similar finding were reported for 4vHPV vaccination in boys [82]. However, some women still report suspected adverse events. Therefore, Lützen conducted a study to examine the association between psychiatric conditions, general practitioner attendance, and indicators of psychological

symptoms prior to 4vHPV vaccination and the risk of referral to an HPV centre following vaccination [83]. They concluded that women with suspected adverse events after vaccination more often had pre-existing psychiatric conditions, psychological symptoms, or frequent GP attendance prior to HPV vaccination. In addition, Weye et al found a social inequality in the referral to a diagnostic centre following HPV vaccination [84]. This might be explained by an increased morbidity in girls and women of lower socioeconomic status. The results of these studies suggest that factors prior to vaccination are associated with the risk of reporting suspected adverse events.

5.4.2 Other potential future target disease

5.4.2.1 Meningococcal B

Two case reports have been published about a probable relationship of meningococcal B vaccination with toxic epidermal necrolysis [85] or urticarial vasculitis [86]. Another case report described a case of 4CMenB vaccine failure in a young adult receiving eculizumab for atypical haemolytic uremic syndrome [87].

Other studies demonstrated an acceptable safety profile of 4CMenB when administered to infants, children and adolescents [88-92] or hospitalised premature infants [93], although a significant difference in all-cause fever consultation rates in vaccine-eligible infants was found in the UK (IRR 1.58; 95% CI 1.22-2.05 in the 7-10 week olds and IRR 1.47; 95% CI 1.17-1.86 in the 15-18 week-olds)[94]. Furthermore, the introduction of 4CMenB vaccination in the UK was associated with increased rates of AEFIs per 1,000 immunisation episodes from 1.0 to 3.4 ($p<0.001$) at 2 months and from 0.14 to 1.13 ($p=0.005$) at 4 months. At 3 months, when 4CMenB is not given, no increase was seen ($p=0.380$). 4CMenB introduction was also associated with increased AEFI-related hospital admissions, invasive investigations, and intravenous antibiotic use [95]. It is worth noting that this reactogenicity profile has not been associated with severe outcomes to date [96]. In addition, in response to two university outbreaks, no safety concerns were identified [97]. MenB-FHbp vaccine appears to be moderately reactogenic but, overall, it is generally well tolerated, with most adverse reaction being mild to moderate in severity in individuals ≥ 10 years of age [98-100]; these findings have been confirmed in an expert commentary [101].

An investigational combined serogroups ABCWY vaccine showed to be reactogenic, but well-tolerated [102], similar to that of 4CMenB [103].

5.4.2.2 Varicella

Three studies evaluated the safety of a 2-dose varicella vaccination scheme [104-106]. In all studies, the safety profile of this scheme was well tolerated, with no increased risk of febrile seizures after the second dose [104], although the incidence of grade 3 redness and swelling of any intensity was significantly higher [105]. No evidence was found of an increased risk of arterial ischaemic stroke [107] and of major birth defects [108] following varicella vaccination. Furthermore, no serious side effects occurred in immunosuppressed patients [109, 110], especially when cellular and humoral immunologic measures are within clinically acceptable levels [111]. Several reviews confirm these conclusions [112-115].

The safety of two new vaccines (Varivax manufactured using a new seed manufacturing process, and Bio Pox was demonstrated in two trials [116, 117].

5.4.2.3 *Herpes Zoster*

Many studies have demonstrated the safety of live-attenuated Herpes Zoster vaccination [118], even in concomitant administration of pneumococcal vaccination [118] or quadrivalent influenza virus vaccination [120]. Transient injection-site reactions, herpes zoster, and rashes were most frequently reported following herpes zoster vaccination [121, 122]. Live-attenuated herpes zoster vaccination also appeared to be safe in immune compromised patients [5, 6, 123, 124], patients with rheumatoid arthritis [125, 126], inflammatory bowel disease patients being treated with anti-TNF medications [127], and patients with end-stage renal disease (Miller [128]). For the new herpes zoster subunit (HZ/su) vaccine, no safety concerns have been identified in immunocompetent as well as in immunocompromised people [129-134]. The safety of an investigational inactivated zoster vaccine was found in adults with autoimmune disease treated with immunosuppressive therapy [135].

5.4.2.4 *Hepatitis A*

In the past year, only one study has been published concerning the safety of hepatitis A vaccine. This showed that two doses of inactivated hepatitis A vaccine were well tolerated in most immunosuppressed children with juvenile idiopathic arthritis (Maritsi [136]).

5.4.2.5 *Hepatitis B*

A review of current US-licensed Hepatitis B vaccines administered alone or in combination with other vaccines did not reveal new or unexpected safety concerns [137], even when administered in haemodialysis patients [138] or pregnant women [139]. However, disproportionality analyses of the same database showed that MS cases were up to five times more likely to be reported after a hepatitis B vaccination than after any other vaccination, although this kind of analysis is mainly suited for hypothesis generation. Besides that, numerous studies already have evaluated a possible relationship between hepatitis B vaccination and MS [140-143]. A large body of scientific evidence now shows that hepatitis B vaccination does not cause or worsen MS. Other studies demonstrated that HBsG-1018, HBsAg-Eng, mpHBV, Heptavax-II and a new HBAI20 vaccine were well-tolerated [144-147].

5.4.2.6 *Rotavirus*

Several studies showed the favourable benefit-risk balance for RV1 [148, 149] and RV5 [150, 151], even in the neonatal period [152]. In a review about the status of rotavirus recommendations across Europe, it was also concluded that more than 10 years after their introduction, available data confirm the benefits and acceptable safety profile of infant rotavirus vaccination [153], although more studies are needed that confirm the safety of rotavirus vaccines in large numbers of preterm infants [154].

New vaccines such as parenteral trivalent P2-VP8-P subunit vaccine and the live attenuated Rotavac and RotaSIIL vaccines are well tolerated [155-158]. Parenterally administered rotavirus vaccines have the potential to reduce safety concerns associated with live oral rotavirus vaccines [159]. In a phase I study, a liquid formulation of RotaSIIL (LBRV-PV) was also found to be safe and well tolerated in adults [160].

For post-marketing surveillance, a background intussusception incidence of 112.9 per 100,000 children aged <2 years was determined in China [161]. This is considerable higher than the background rates found in developed countries [162-164].

5.5 Literature

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*RIVM publication

6
Various research topics addressing evaluation of the NIP in a broader sense

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6.1 Key points

- Data collection of the third seroepidemiological study (PIENTER-3) ended in 2017. In total, 7,623 serum samples were collected.
- The response of PIENTER-3 (blood and questionnaire) was 14.4% for the national sample and 19.8% in the sample of low vaccination coverage areas. Almost half of the participants also donated oro- and nasopharyngeal swabs, faeces and an additional questionnaire.
- A lower rate of admission to hospital with infection after MMR vaccination was observed, but could at least partly be explained by healthy vaccinee bias. The lower rate was associated with receipt of any additional vaccine, not specifically MMR vaccine.
- The rising expenses of vaccination programmes are an important point of discussion. A good understanding of these evolving expenses is important for current debates on whether to include a new vaccine.

6.2 Tables and figures

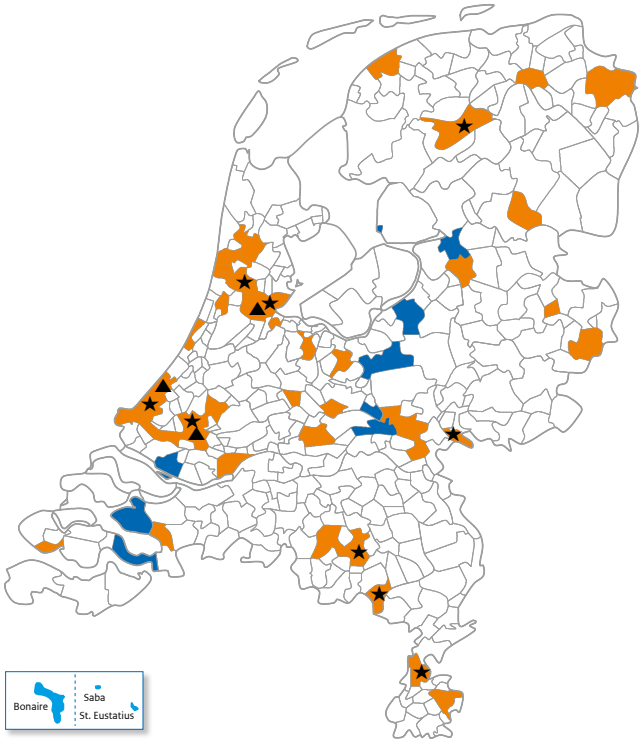

Figure 6.1 Overview of included municipalities for the PIENTER-3 study

Municipalities depicted in blue are low vaccination coverage areas.

★ indicate a municipality with oversampling of non-Western migrants.

▲ indicate municipality with additional oversampling of people with migration background from Suriname, Aruba and the former Dutch Antilles.

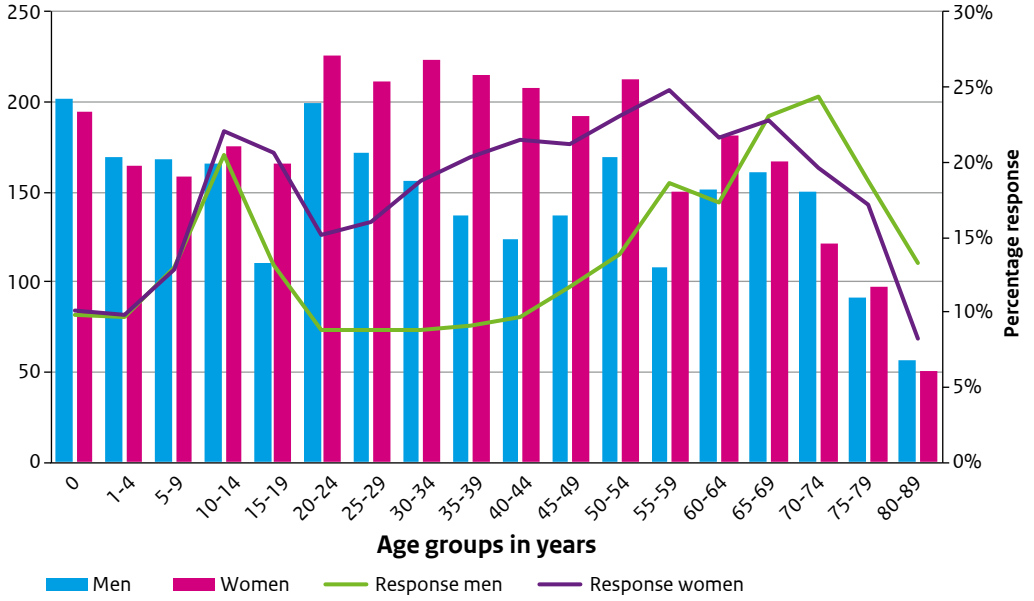

Figure 6.2 Overview of number of participants of the national sample and oversampling of non-Western migrants of the PIENTER-3 study

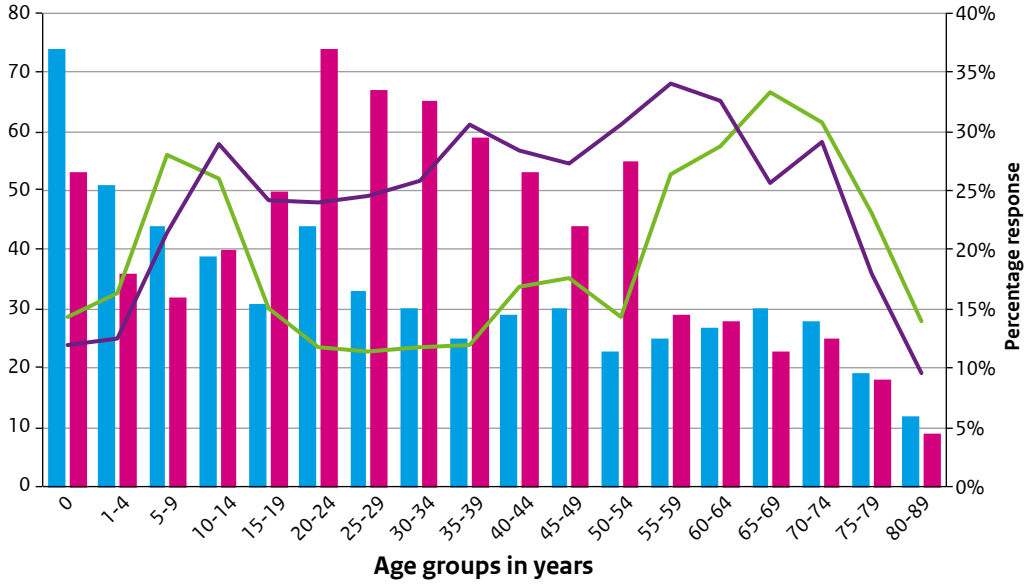

Figure 6.3 Overview of number of participants of the low vaccination coverage sample of the PIENTER-3 study

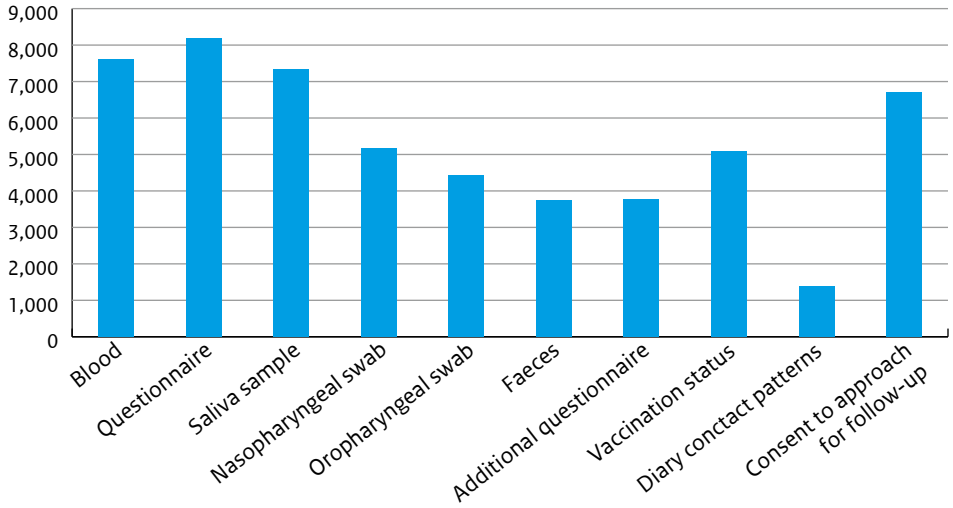

Figure 6.4 Overview of the total number of materials collected in the PIENTER-3 study (from participants of the national sample, oversampling of non-Western migrants, low vaccination coverage area sample and the extra persons with a migration background from Suriname, Aruba and former Dutch Antilles)

Table 6.1 Overview of response per sample in the PIENTER-3 study

	NS + oversampling of non-Western migrants	LVC sample	SAN sample
Response (Blood+Questionnaire)	5,745 (14.4%)	1,354 (19.8%)	501 (6.9%)

NS=National sample; LVC=low vaccination coverage; SAN=persons with a migration background from Suriname, Aruba and former Dutch Antilles.

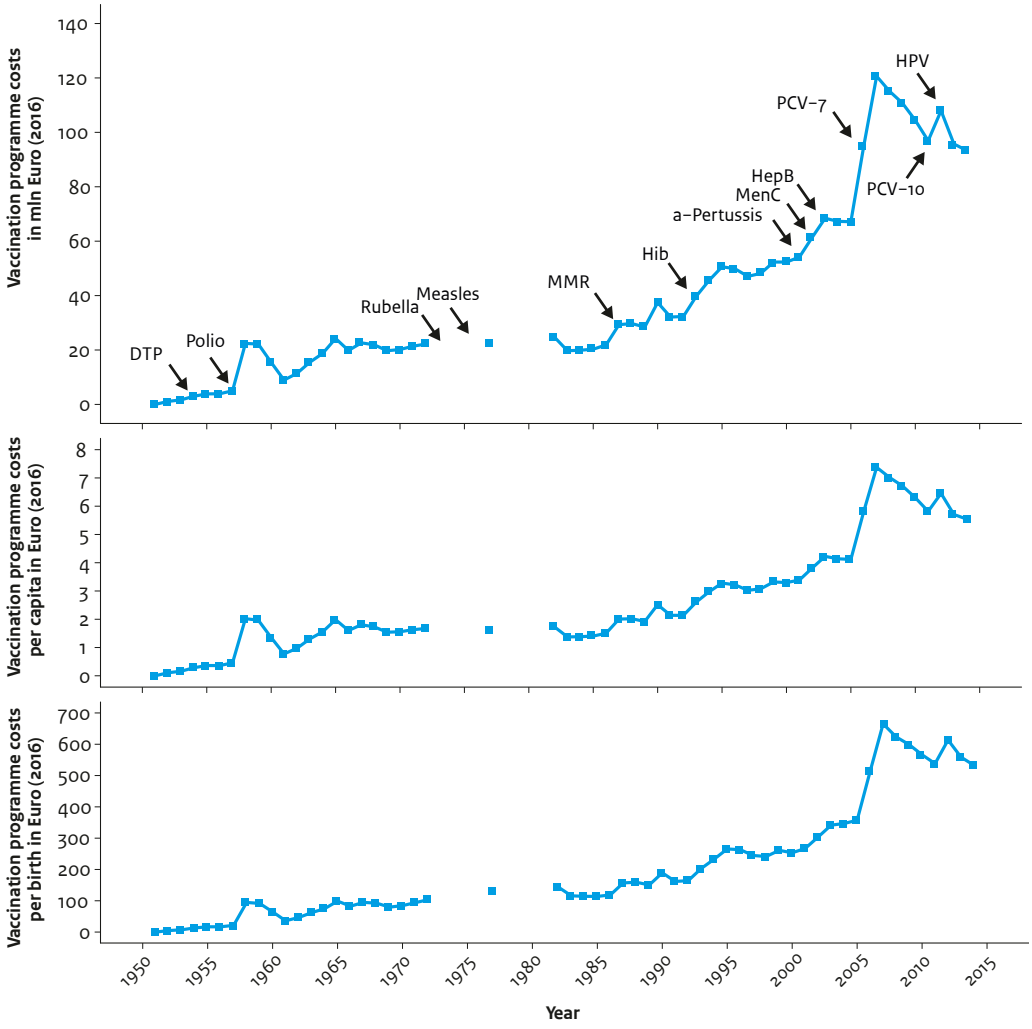

Figure 6.5 Government expenditure on the Dutch NIP and influenza vaccination programme, 1951-2014, the Netherlands

All costs are expressed in Euro (2016) adjusted for inflation using Consumer Price Indexes. All prices express government expenditure according to various official reports. Data for the periods 1973-1976 and 1978-1981 are unavailable.

DTP-IPV=diphtheria-tetanus-pertussis-inactivated poliomyelitis; rubella, only for 11-year-old girls up to 1987; MMR=measles-mumps-rubella, for both boys and girls aged 14 months and 9 years; Hib=Haemophilus influenza serotype b; a-Pertussis=acellular-pertussis; MenC=meningococcal C; HepB=hepatitis B; PCV-7=7-valent pneumococcal conjugate vaccine; PCV-10=10-valent pneumococcal conjugate vaccine; HPV=human papillomavirus.

6.3 Immunosurveillance: PIENTER-3

Regular national seroepidemiological (PIENTER) studies are performed in order to obtain insights into the age-specific seroprevalence of NIP-targeted diseases in the Dutch general population. The first survey was performed in 1995–1996 (n_{blood}=9,948; 0–79 years) and the second in 2006–2007 (n_{blood}=7,904; 0–79 years) [1, 2]. The third population-based cross-sectional seroepidemiological study was performed from February 2016 to October 2017 [3]. A detailed description of the study and the methodology is described in previous reports [4, 5]. In short, data (blood, oral fluid sample and questionnaire) were collected from the general population (national sample, 40 municipalities) and from nine low vaccination coverage (LVC) areas (age strata 0, 1–4, 5–9, ..., 75–79, 80-89 years). Non-Western migrants were oversampled in nine of the municipalities in the nationwide sample, and in three municipalities an extra subset of persons with a migration background from Suriname, Aruba and former Dutch Antilles (SAN) were sampled (Figure 6.1). Participants could optionally donate nasopharyngeal and oropharyngeal swabs, a faecal sample, and complete an additional questionnaire.

In total, 5,745 (response 14.4%, range 4.9-21.9%) participants donated sera in combination with a questionnaire in the nationwide sample. Of the 5,745, 601 were derived from the extra sampling of non-Western migrants immigrants (response 7.3%). 46.7% (N=2,682) fully participated in the additional part of the study (i.e. nasopharyngeal- oropharyngeal swabs, faecal samples, and an additional questionnaire). Figure 6.2 shows the number of participants with sera and questionnaire per age strata stratified by sex in the national sample, including non-Western migrants.

In the LVC sample we obtained sera and a questionnaire from 1,354 participants (response 19.8%, range 15.0%–26.3%). Of these, 674 (49.8%) donated all materials of the additional part. The number of participants included per age strata stratified by sex in the LVC areas is shown in Figure 6.3.
In the SAN sample, a combination of sera and questionnaire was obtained from 501 participants (response 6.9%, range 5.8%-8.3%). In total, more than 500 0-year-olds and 100 participants aged 80-89 were included in this study. An overview of all collected materials is given in Figure 6.4.

Laboratory analyses have now started and the first serological results are expected at the end of 2018. These data will give crucial insights into (the evaluation of) the Dutch NIP, and will be essential in future outbreak management and possible changes in the NIP.

6.4 Non-specific effects of vaccination

As part of the RIVM's strategic programme (SPR), non-specific effects of vaccination are currently being investigated. In addition to protecting against target diseases, vaccines may also protect against other infectious diseases – so-called 'non-specific effects'. The majority of evidence for non-specific effects of MMR and DTP containing vaccines originates from studies in low-income countries, which have high rates of infant mortality due to infectious diseases.

The public health relevance of non-specific effects of vaccines in high-income countries, which have low infant mortality rates, is largely unknown.

Previously, the risk of infectious disease related hospital admissions was compared between children having received the DTP-containing vaccine as most recent vaccine versus children having received the MMR vaccine as most recent vaccine in a population-based nationwide cohort study of almost 900,000 Dutch children born between 2005 and 2011 [6]. The conclusion was that healthy vaccinee bias could at least partly explain the observed lower rate of admission to hospital with infection after MMR vaccination. The lower rate was associated with receipt of any additional vaccine, not specifically MMR vaccine.
Currently, a similar analysis is being performed with GP consultations as outcome rather than hospital admissions. Results are expected at the end of 2018.

In Denmark, a randomised trial was performed to assess the effect of BCG vaccination at birth on all-cause hospitalisation [7]. A secondary outcome of this trial was hospitalisation for infection. A total of 4,262 children were assigned to either receive the BCG vaccine or not and were followed through the Danish National Patient Register. There was no difference in risk of hospitalisation for infection up to 15 months of age; in both groups the mean number of hospitalisations per child was 0.28 resulting in a hazard ratio of 0.99 (95%CI 0.85-1.15). The effect of BCG on hospitalisation for infection was significantly modified by BCG vaccination of the mother (HR 0.65 (0.45-0.94) for BCG vaccination mother), caesarean delivery (HR 0.73 (0.54-0.99) for children born by caesarean section) and prematurity (HR 1.81 (0.95-3.43) for premature children). In conclusion, BCG vaccination at birth did not reduce the risk of hospitalisations for infections in this high-income setting.

6.5 Historical overview of government expenditure on vaccinations

The rising expenditure on vaccination programmes is an important point of discussion. This is especially the case when deciding on whether to include a new vaccine. Cost evaluations are therefore an important part of vaccine research. This was not always the case. Costs were barely a point of discussion when the first nationally organised vaccination programmes were implemented, such as those against diphtheria, pertussis, tetanus and polio. To obtain better insights into the increasing expenditure on the NIP in the Netherlands, we researched the NIP's financial history [8].

6.5.1 A short history lesson

Officially the NIP was launched in 1957 with the vaccination against polio. However, organised vaccination efforts against diphtheria, pertussis and tetanus, had been organised from 1953. Vaccinating physicians were paid from the so-called "Praeventiefonds". Since 1953, vaccines were made available free of charge by the government. In that period, the total budget amounted to 500,000 Dutch guilders. The organisation of the NIP was scattered, and many parties were involved. This changed in 1955 after efforts were made to centralise the NIP resulting in the first "entgemeenschappen", which were further developed, leading to the polio vaccinations in 1957. The "Praeventiefonds" continued to support the NIP until 1963, when the

Ministry of Social Affairs and Public Health took on complete financial responsibility. In 1974, finances were secured through the "Algemene Wet Bijzondere Ziektekosten". This lasted until 2015, when this law was abolished. Currently, the NIP is provisioned under terms of the "Wet Publieke Gezondheid" (Public health act).

6.5.2 Government expenditure

We collected information on government expenditure on the NIP from annual reports and records from the Ministry of Public Health and preceding organisations, as well as those of the "Praeventiefonds". All expenses were recalculated to Euros in 2016. Figure 6.5 shows the results. In general, the costs have increased substantially since the start of the NIP, from €5 million in 1957 to €93 million in 2014. The inclusion of an increased number, and of more expensive vaccines like the 7-valent pneumococcal vaccine in 2006 resulted in a sharp increase in costs, from €67 million in 2005 to €130 million in 2007. However, per capita and per birth, the costs are minimal, at €5.54 per person and €533 per birth in 2014.
While the expenses presented are likely to be incomplete and do not reflect the total costs (the execution of the NIP and catch-up campaigns may not be included), they do provide a clear picture of the development of expenditure on vaccines. A good understanding of these evolving expenses is important for current debates on the decision to include new vaccines.

6.6 Literature

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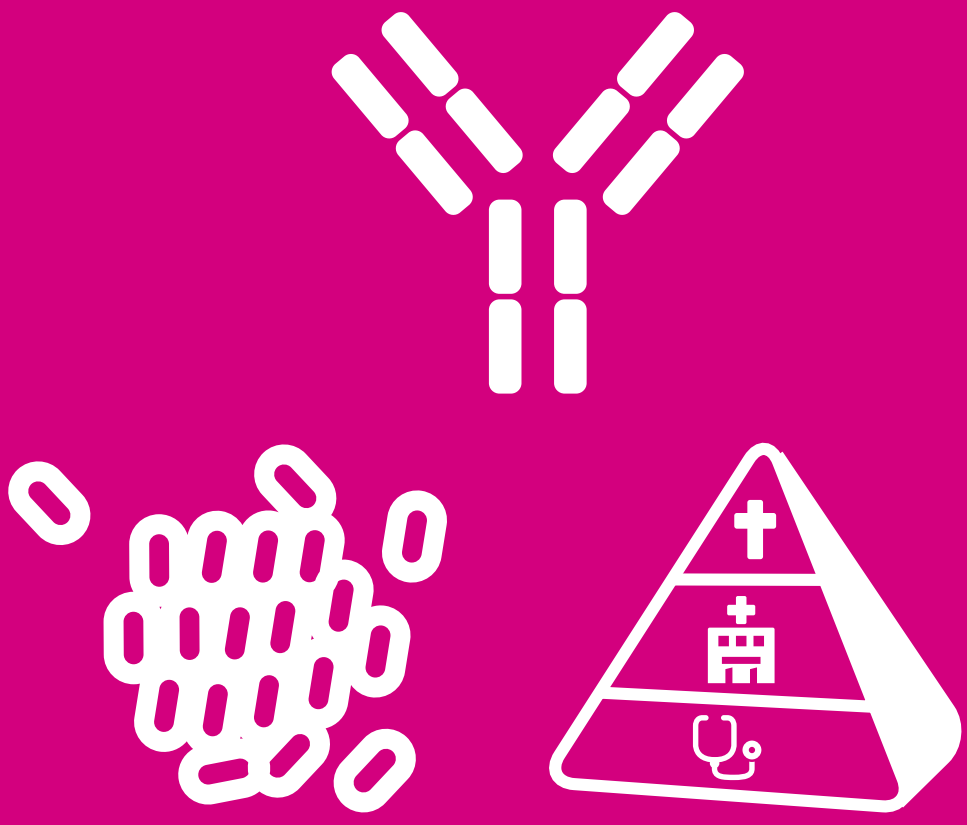
*RIVM publication

7
Current National Immunisation Programme



7.1 Diphtheria

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

7.1.1 Key points

- In 2017, four diphtheria cases were notified.
- In 2018 up to July 1, one diphtheria case has been notified.

7.1.2 Tables and figures

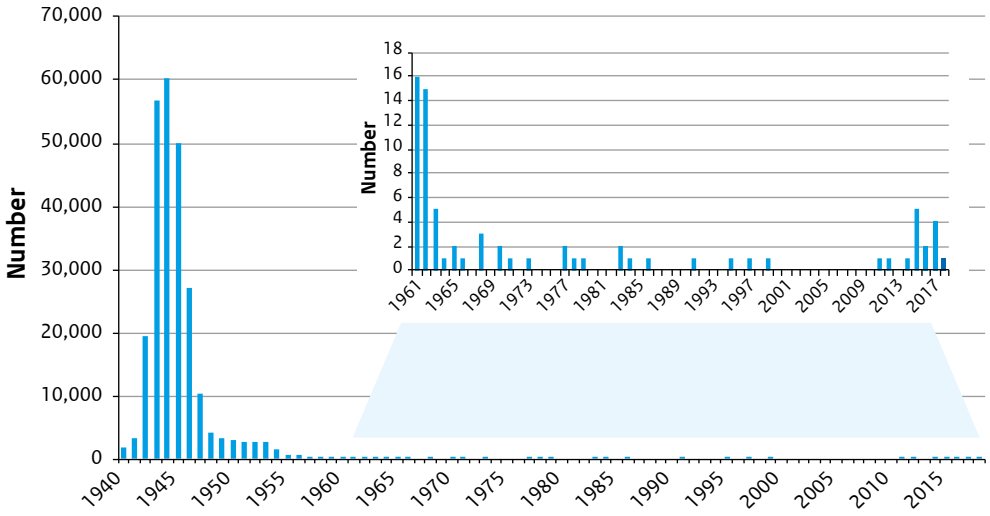


Figure 7.1.1 Diphtheria notifications per year 1940-1960 (left part) and 1961-2018*(right part)
* reports up to July 1, 2018 are included

Table 7.1.1 Laboratory results of tested Corynebacterium strains for 2015-2018*. Date of laboratory test is used for year of classification.

	Corynebacterium diphtheriae				*Corynebacterium ulcerans*			
	PCR negative	PCR positive	Elek positive	Elek non-conclusive	PCR negative	PCR positive	Elek positive	Elek non-conclusive
2015	8	1	1	NA	0	2	1	1
2016	12	1	1	NA	2	1	NA	1
2017	9	1	0	0	0	2	NA	2
2018*	3	1	1	NA	2	0	NA	NA

* Up to July 1, 2018
NA = not applicable

7.1.3 Epidemiology

In 2017, four diphtheria notifications were received (Figure 7.1.1). An unvaccinated woman born in 1963 was reported with respiratory diphtheria caused by *Corynebacterium ulcerans.* Her dog was the probable source of infection. The remaining three notifications (all vaccinated) concerned cases of cutaneous diphtheria. Cases were born in 1963, 1966 and 1993. Two of those, caused by *C. diphtheriae*, had a travel history to Asia.

7.1.4 Pathogen

In 2017, the RIVM received 12 *C. ulcerans* or *C. diphtheriae* strains, most with the suspicion of cutaneous diphtheria and 1 from respiratory samples.
Likewise, in 2018 up to July 1, RIVM received 6 *C. ulcerans* or *C. diphtheriae* strains, all with suspicion of cutaneous diphtheria. One *C. ulcerans* strain was PCR and Elek-test positive, from a patient born in 1966 without travel history. Date of disease onset of this case was in 2017.
See Table 7.1.1 for details on laboratory results for the respective strains.

7.1.5 International developments

In 2017, four countries in the Region of the Americas (Brazil, the Dominican Republic, Haiti and the Bolivarian Republic of Venezuela) reported confirmed diphtheria cases due to decreasing vaccination coverage. This outbreak continued in 2018 in Colombia, Haiti and the Bolivarian Republic of Venezuela.

7.2 *Haemophilus influenzae* disease

M.J. Knol, A. van der Ende, J. van den Boogaard, P. Kaaijk, G. Berbers, H.E. de Melker

7.2.1 Key points

- In 2017, the number of cases of *Haemophilus influenzae* type b (Hib) disease was similar to 2016 (46 vs 44 cases). Up to May 2018, 16 cases have been reported.
- In 2017, the incidence of Hib disease was highest among children aged under 5 years (1.6 per 100,000). The incidence in 2017 was lower than in 2016 (2.4 per 100,000; n=21), so the increasing trend observed from 2011 to 2016 did not continue in 2017.
- There were 11 Hib cases with vaccine failure (61% of all vaccine eligible Hib cases) in 2017, resulting in a Hib vaccine effectiveness estimate of 93%, similar to previous years.
- In 2017, more cases of nontypeable Hi (NTHi) disease were reported than in 2016 (159 vs. 124). Up to May 2018, 91 cases have been reported; higher than in the same period in 2017 (80 cases) or 2016 (61 cases), confirming a continuing increase in NTHi disease.

7.2.2 Figures

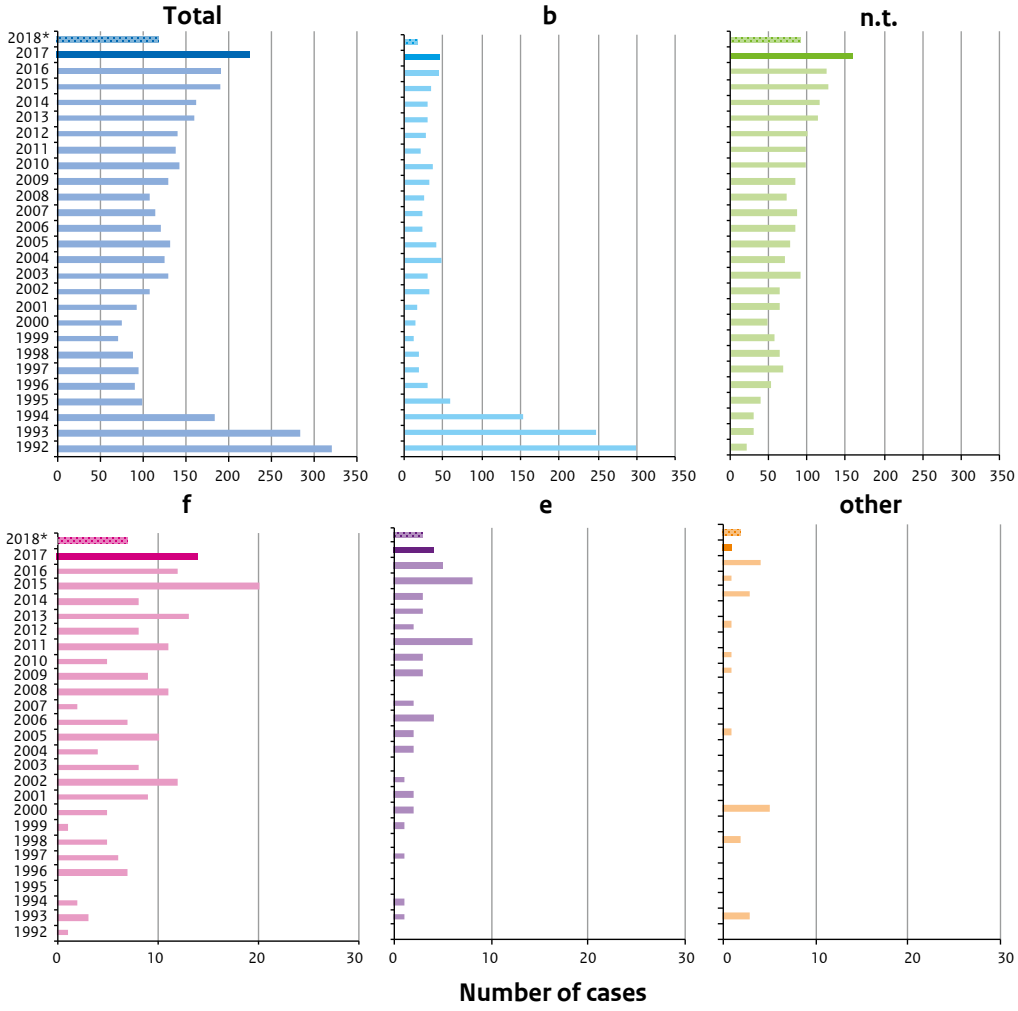


Figure 7.2.1 Number of *Haemophilus influenzae* cases per serotype, 1992-2018* (*up to May)
Source: NRLBM

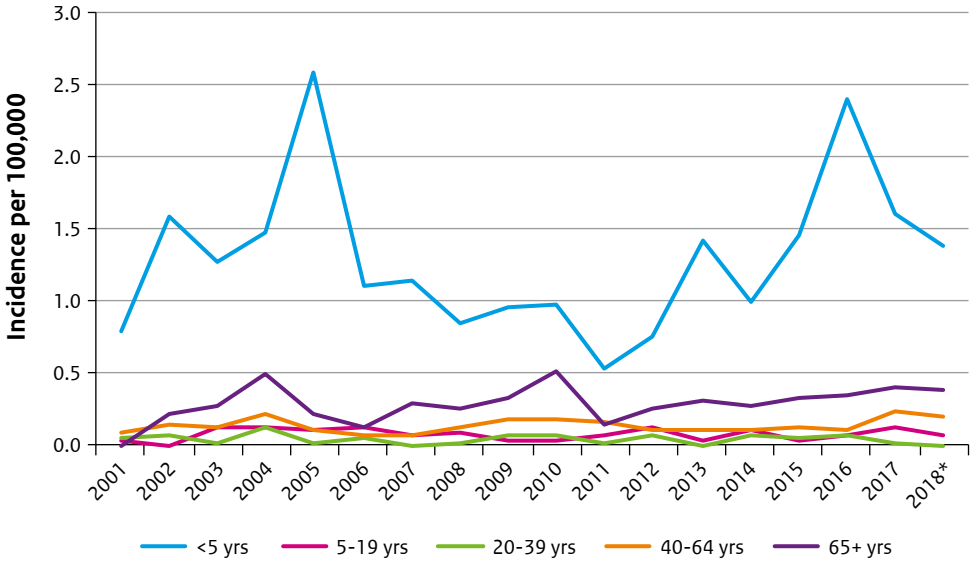


Figure 7.2.2 Age-specific incidence of *Haemophilus influenzae* type b (Hib) disease, 2001-2018* (*up to May)

Source: NRLBM

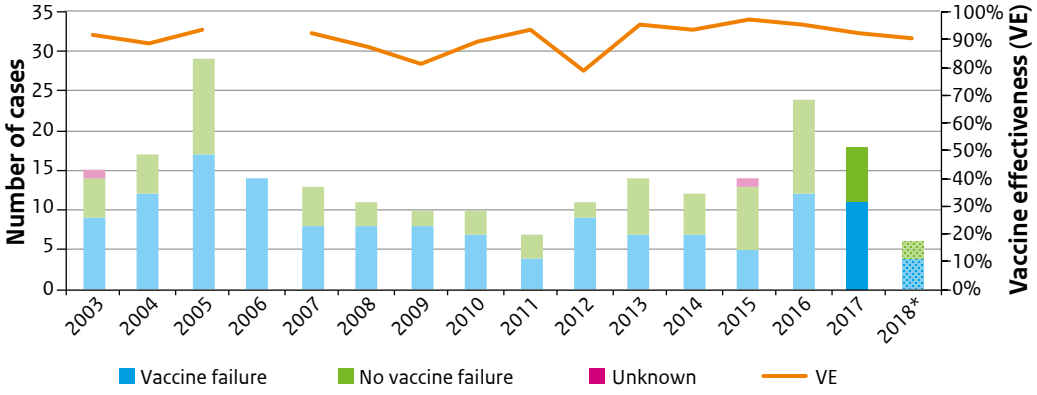


Figure 7.2.3 Number of *Haemophilus influenzae* type b (Hib) cases in cohorts eligible for vaccination (i.e. born after April 1, 1993) by vaccine failure and estimated vaccine effectiveness, 2003-2018* (*up to May)

Source: NRLBM, Praeventis, Osiris

7.2.3 Epidemiology

7.2.3.1 *Hib disease*

7.2.3.1.1 *Incidence*

In 2017, the number of Hib cases was 46 (incidence: 0.27 per 100,000), similar to 2016 (n=44; incidence: 0.26 per 100,000), so no further increase in cases was seen (Figure 7.2.1). The incidence was highest in children aged under 5 years (1.6 per 100,000; n=14) (Figure 7.2.2). The incidence in this age group was lower in 2017 than in 2016 (2.4 per 100,000; n=21), so the increasing trend observed from 2011-2016 did not continue in 2017. Up to May 2018, 16 Hib cases have been reported, of which five were aged under 5 years.
Outcome status was known for 27 and 9 cases in 2017 and 2018, respectively. Of these, one patient, a 7-month-old unvaccinated baby, died in 2017.

7.2.3.1.2 *Vaccine failure*

In 2017 and 2018 (up to May), 18 and 6 Hib cases were reported among cohorts eligible for vaccination, respectively (Figure 7.2.3). Of these, 11 (61%) and 4 cases (67%) were vaccine failures (i.e. received at least two vaccinations with at least two weeks between the second vaccination and date of diagnosis). Ten vaccine failure cases were aged under 5 years, and five were older than 5 years. Information on underlying disease was available for 12 of the 15 cases with vaccine failure. Three of these cases (25%) had an underlying disease. Of the 18 and 6 Hib cases eligible for vaccination in 2017 and 2018 (up to May), 1 case was vaccinated once and 8 cases were unvaccinated. The unvaccinated children were between 3 and 24 months old. None of the unvaccinated children had an underlying disease (known for 6 cases).

7.2.3.1.3 *Vaccine effectiveness*

The estimated vaccine effectiveness (VE) of Hib vaccination using the 'screening method' was 93% (95%CI 81-97%) in 2017 and 91% (95%CI 49-98%) in 2018 (up to May) (Figure 7.2.3). The overall VE for 2003-2018 was 92% (95%CI 89-94%).

7.2.3.2 *Nontypeable Hi (NTHi) disease*

In 2017, 159 cases of NTHi were reported, more than in 2016 (124 cases) (Figure 7.2.1). Up to May 2018, 91 cases have been reported, more than in the same period in 2017 (80 cases) or 2016 (61 cases), confirming a continuing increase in NTHi disease. In 2017, the incidence was still highest among elderly aged 65 and older (2.7 per 100,000; n=84) and children aged under 5 years (2.1 per 100,000; n=18). This increasing trend can also seen in other European countries [1]; reasons for this could be population aging, increased use of immunosuppressive therapy, or increased reporting. Another possible reason is strain replacement due to introduction of Hib vaccination, however no clear evidence is available for this [2].

7.2.3.3 *Disease due to other Hi serotypes*

In 2017, four Hi cases with serotype e (Hie) were reported, similar to previous years (Figure 7.2.1). Up to May 2018, three Hie cases have been reported. In 2017, 14 cases of Hif were reported, comparable to previous years (Figure 7.2.1). Up to May 2018, 7 Hif cases have been reported. In 2017 and 2018 (up to May), three Hi cases with serotype a have been reported (Figure 7.2.1).

7.2.4 Pathogen

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

7.2.5 Research

The current NIP may provide insufficient protection for premature children, given their immature immune system. Currently, approximately 15,000 premature babies are born per year in the Netherlands. In a prospective observational study (PRIEMA study) of 300 premature children distributed over 3 gestational age groups (< 28, 28-32 and 32-36 weeks) the serological immune response after the routine vaccination schedule was determined in order to explore if the current schedule is optimal for this specific group. Blood samples were collected at 6 weeks (pre-vaccination), at 5 months (post-primary series), and at 12 months (post-booster). After preliminary analysis of the first 157 serum samples of the post-primary series, 54% (85/157) had insufficient protection against Hib (< 0.15 µg/ml). After the booster vaccination, this percentage of protection by sufficient antibody levels was much higher. Protection against diphtheria, tetanus and pertussis was sufficient after both the primary series and the booster. Analysis of all data is expected to be completed early in 2019.

Before 2009, invasive Hib disease in the Netherlands was surveilled using data from the national reference laboratory for bacterial meningitis (NRLBM), which types Hi isolates from normally sterile sites (e.g. blood and cerebrospinal fluid) sent in by clinical microbiology laboratories (CMLs). In 2009, a mandatory notification system for laboratory-confirmed Hib cases from CMLs and clinicians to municipal health services (GGDs) was added to monitor vaccine effectiveness and improve surveillance data on vaccination status, morbidity and mortality. Data from the two sources are linked on year of birth, municipality and notification date. The completeness of notification for Hib cases notified between 1-1-2009 and 31-12-2017 was assessed by analysing the complementarity of both surveillance systems. Of 355 cases, 53 (15%) were notified by GGDs only, 156 (44%) appeared in the NRLBM system only, and 146 (41%) were in both systems. Of the 53 cases, 31 (58%) notified by GGDs only appeared to be typed as non-b at the NRLBM and were thus misclassified by GGDs, and 22 cases (42%) were of unknown type (no isolate received at NRLBM). One GGD notified 6 of the 22 cases. The CML involved explained that although they notified the cases to the GGD, they had doubts about sending the corresponding isolates to the NRLBM because the isolates were obtained from blood and not from cerebrospinal fluid. Cases registered in the NRLBM only were older than cases notified by both systems (median age 56 (range 0-99) versus 6.5 (0-86) years; $p<0.001$). Isolates in the NRLBM system only were more often obtained from blood than cerebrospinal fluid compared to isolates present in both systems (88% versus 69% obtained from blood, $p<0.001$). Fifteen of 69 CMLs sending Hi isolates to the NRLBM did not notify any case to the GGD. Three CMLs from which the NRLBM obtained at least 8 Hib isolates that were not notified to GGDs, were asked why GGDs were not informed. Explanations included: uncertainty about notifying non-meningitis cases to GGD; forgot to notify; and technical problems with the digital notification system. Morbidity/mortality/vaccination data was unknown for cases registered in the NRLBM system only, but known for 100%/91%/100% and 100%/98%/100% of cases notified by GGDs only, by both GGDs, and NRLBM, respectively. It was concluded that despite mandatory notification, GGDs were informed in about half of all

invasive Hib cases. This impacts on completeness of the national Hib surveillance data and may result in missing opportunities for chemoprophylaxis usually advised by GGDs (if applicable). It is recommended that GGDs review notification criteria with CMLs to emphasise the necessity of reporting all invasive Hib disease cases.

7.2.6 International developments

Collins et al. present data from a national UK serosurvey performed in 2013-2014 determining Hib antibody levels in children aged up to 8 years [3]. They also reported on the current epidemiology of invasive Hib disease in England and Wales. IgG concentrations were highest in 1-year-olds (after the 12-month booster vaccination) and then declined rapidly. Overall, 89% of children (719/817) had Hib IgG concentrations ≥0.15 µg/mL, the putative threshold for short-term protection against invasive Hib disease. In the period 2012–2016, the annual Hib disease incidence remained below one case per million population. There were only two deaths over the five-year period (case fatality rate, 3.0%).

7.2.7 Literature

7.2.7.1 References

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7.2.7.2 Recent RIVM publications

1. Monge S, Hahné SJ, de Melker HE, Sanders EA, van der Ende A, Knol MJ. Effectiveness of the DTPa-HBV-IPV/Hib vaccine against invasive *Haemophilus influenzae* type b disease in the Netherlands (2003-16): a case-control study. Lancet Infect Dis. 2018 May 8.
2. Monge S, Mollema L, de Melker H, Sanders E, van der Ende A, Knol M. Clinical Characterization of Invasive Disease Caused by *Haemophilus influenzae* Serotype b in a High Vaccination Coverage Setting. J Pediatric Infect Dis Soc. 2018 Mar 22.

* RIVM publication

7.3 Hepatitis B

I.K. Veldhuijzen, M. Visser, F. van Heiningen, A. Suijkerbuijk, B. van Benthem, J. Cremer, K.S.M. Benschop, A.J. King

7.3.1 Key points

- Of the total number of 1236 reported hepatitis B cases in 2017, 9% had an acute infection and 89% a chronic infection.
- The incidence of acute hepatitis B notifications remained stable at 0.7 per 100,000 population.
- Among both men and women, heterosexual contact was the most frequently reported risk factor for acute HBV infection.
- In 2017, genotype A continued to be the dominant genotype among acute HBV cases with 62% of 76 genotyped cases, followed by genotype D (12%).
- After declining for seven consecutive years, the number of newly diagnosed chronic HBV infections increased by 12% to 1105 in 2017, corresponding to an incidence of 6.5 per 100,000 population.
- Ninety-one percent of people with a chronic HBV infection were born abroad. In contrast, 79% of people with an acute HBV infection were born in the Netherlands.

7.3.2 Tables and figures

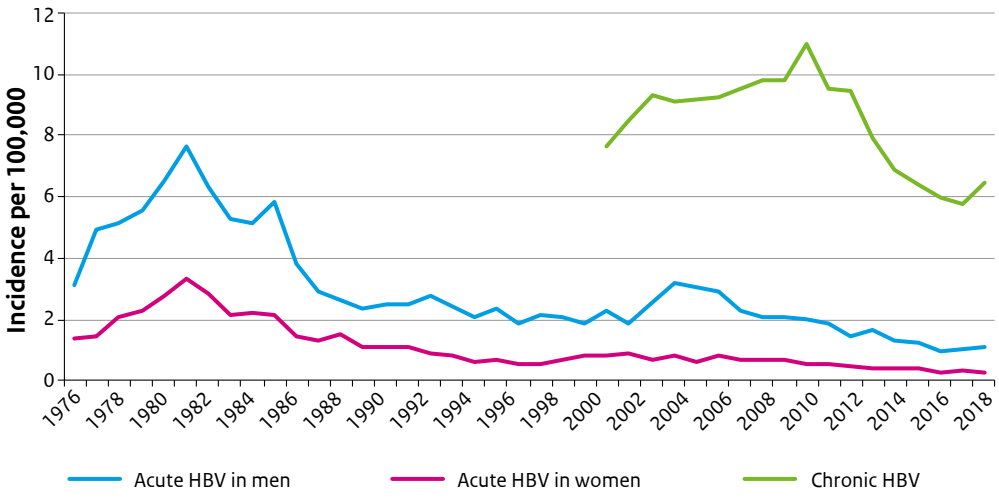

Figure 7.3.1 Incidence of acute HBV infections in men and women in the Netherlands from 1976 and chronic HBV infections from 2000

Source: Osiris

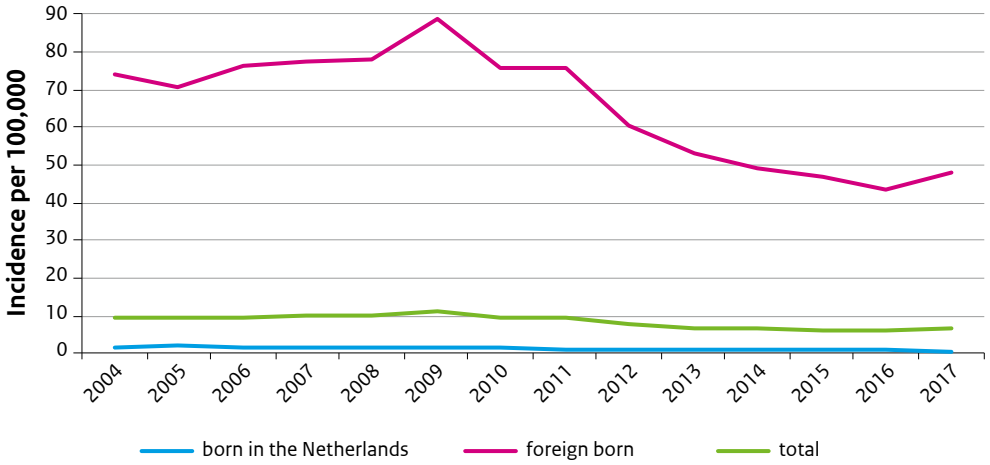

Figure 7.3.2 Incidence of chronic HBV infections in the Netherlands between 2000 and 2017 by country of birth

Source: Osiris

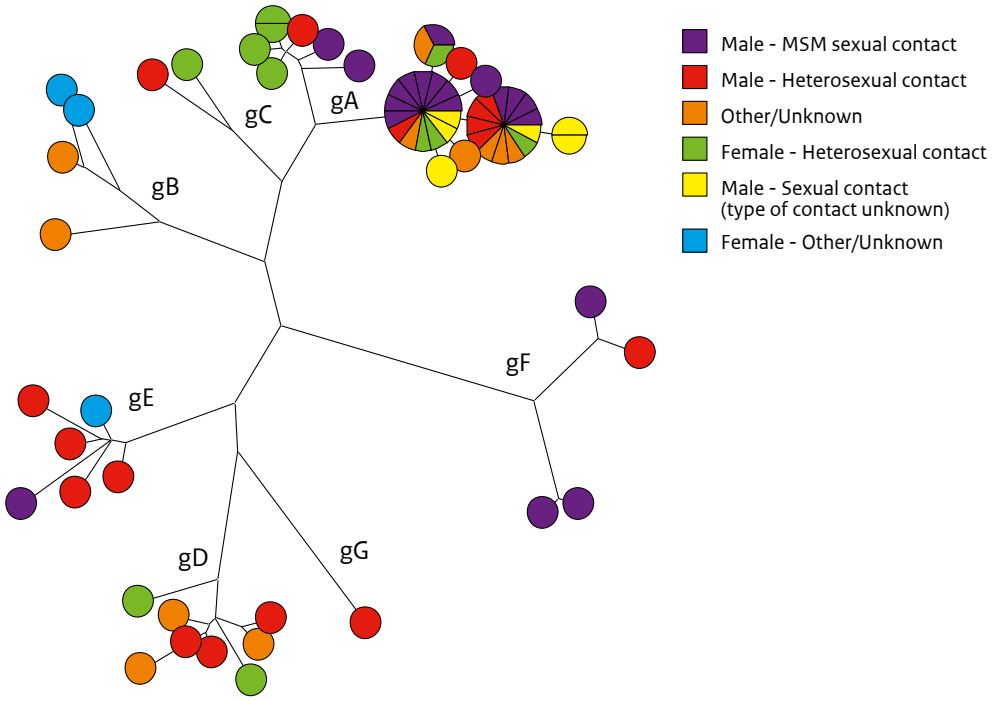

Figure 7.3.3 Optimised maximum parsimony tree based on the full length sequence of acute HBV cases in the Netherlands in 2017 by reported transmission route (n=64). gX: genotype

7.3.3 Epidemiology

In 2017, 1236 cases of hepatitis B virus (HBV) infection were notified. Of these, 1105 (89%) were chronic infections and 115 (9%) acute infections (16 cases unknown status).

7.3.3.1 Acute HBV epidemiology

The number of notified acute HBV infections in 2017 is comparable to 2016 (111 cases). In the first half of 2018, 38 cases of acute HBV were reported. The incidence of acute HBV notifications in 2017 was 0.7 per 100,000 population, 1.1/100,000 among men and 0.3/100,000 among women. The HBV incidence seems to have stabilised after having declined for both men and women since 2004 (Figure 7.3.1). The age at infection has increased over time, however it did not increase further last year. The mean age of patients with acute HBV infection was 44.7 years in 2017 and is higher in men (45.8) than in women (40.5). No cases of acute hepatitis B were reported among young children; the youngest patients were aged 17.

In 2017, most cases of acute HBV infection (71%) were acquired through sexual contact. For 15% of the reports of acute HBV infection, the most likely route of transmission remained unknown, despite source tracing. Among men (91 cases), sexual contacts between MSM accounted for 37% of acute infections, with heterosexual transmission accounting for 30%. Among women (24 cases), heterosexual contact accounted for 75% of cases. The majority of patients with acute hepatitis B were born in the Netherlands (79%).

7.3.3.2 Chronic HBV epidemiology

After a decline in the number of chronic HBV notifications over the past seven years, more cases were reported in 2017 (n=1105; incidence 6,5 per 100,000, compared to 980 in 2016) (Figure 7.3.2). Since chronic hepatitis B is largely asymptomatic, the number of new diagnoses is highly influenced by testing practices. The number of people tested for HBV infection annually remains unknown.

In 2017, 91% of the chronic HBV patients where the country of birth was known were born abroad. This proportion has slightly increased over time. The incidence of chronic hepatitis B in people born abroad is 80 times higher than that of people born in the Netherlands (48 compared to 0.6 per 100,000 population (Figure 7.3.2). The number of notifications per country of birth fluctuates over time. In 2017 the most frequently reported countries of birth were China (n=118, 12%), Turkey (n=96, 10%), Syria (n=62, 6%) and Eritrea (n=60, 6%). Around half (53%) of the cases acquired chronic HBV infection through vertical transmission. In one third (33%) of reports of chronic HBV infection, the most likely route of transmission was unknown. Sexual contact was the source of infection of 5%, and for the remaining 10%, transmission may have occurred via other routes such as nosocomial transmission, needle stick injuries, or via injecting drug use (IDU).

7.3.4 Pathogen

Samples are available for genotyping from all acute HBV infections and from chronic infections in MSM and in people detected through the vaccination programme for behavioural risk groups. In 2017, samples were available for molecular typing of 76 acute HBV cases (66%) and

18 chronic HBV cases (2%). PCR amplification and sequencing gave results for 64 (84%) samples of acute HBV infections for the full length genome. An optimised maximum spanning tree of these sequences by the most likely transmission route is shown in Figure 7.3.3. In the Netherlands, 7 different genotypes were found (Genotype A-G). The largest cluster of cases continues to be among genotype A cases, the most common genotype for acute HBV in the Netherlands. Of acute cases with genotype information, 62% were genotype A followed by 12% genotype D. Genotype A was also most common among chronic cases in risk groups (10/18; 56%), followed by genotype E (4/18; 22%).

7.3.5 Research

7.3.5.1 Genetic variation within HBV surface antigen

Genetic variation within hepatitis B surface antigen (HBsAg), in particular within the major hydrophobic region (MHR), is related to immune/vaccine and test failures and can have an impact on the vaccination and diagnosis of acute infection. Molecular analyses to assess genetic variation within HBsAg was done on samples collected between 2004-2014 [1]. The study included virus isolated from 1231 acute and 585 chronic cases, and compared the amino acid variation within the HBsAg between acute and chronic infections. Variation was the highest among chronic strains compared to among acute strains. Both acute and chronic genotype D showed the highest variation compared to other genotypes. Substitutions within the MHR were found in 8.5% of the acute strains and 18.6% of the chronic strains. Specific MHR substitutions having an impact on vaccine/immune escape and/or HBsAg test failure were found among 4.1% of the acute strains and 7.0% of the chronic strains. Additional studies on the impact of these variations on vaccination and test failure need to be conducted, as well as whether HBsAg false-negative variants were missed.

7.3.5.2 Cost-effectiveness of migrant screening for chronic viral hepatitis

Early diagnosis of chronic HBV or HCV infection and linkage to care for antiviral treatment can reduce the burden of chronic hepatitis B and C among migrants in the Netherlands. We assessed the cost-effectiveness of screening foreign-born migrants for chronic HBV and/or HCV by estimating the cost per Quality Adjusted Life Year (QALY) gained [2]. For most migrant populations in the Netherlands, offering combined HBV-HCV screening is cost-effective. The incremental cost-effectiveness ratios (ICERs) range from €5,000/QALY gained for migrants originating from the Former Soviet Union and Vietnam to €9,400/QALY gained for Polish migrants. For migrants originating from Turkey, single HBV screening is the most cost-effective strategy (€6,250/QALY gained). At the Dutch cost-effectiveness reference value of €20,000/QALY gained, HBV and HCV screening proves cost-effective for migrants from countries where chronic HBV or HCV prevalence is as low as 0.41% and 0.22%, respectively.

7.3.5.3 Seroepidemiological study among asylum seekers

We conducted a seroprevalence study among refugees aged 18 to 45 years to assess the level of protection against nine vaccine preventable diseases. In 2016, over 600 refugees from Syria, Afghanistan, Iraq, Iran and Eritrea living in three large asylum-seeker centres participated in the study [3]. Vaccine induced immunity for hepatitis B ranged from 4.8% for participants from Iraq to 34.3% for participants from Iran. Women (29.8%) more often had vaccine induced

antibody levels than men (17.7%, p=0.004). Syrian participants aged 18-25 years, Iranians aged 18-35 years and Afghans aged 36-45 had the highest prevalence of immunity through vaccination (36-39%). Markers indicating resolved or chronic infection (anti-HBc) were most often present in participants from Eritrea (24.5%) and least often in participants from Iran (4.6%). Seven participants had a chronic HBV infection: of these, three were from Eritrea (HBsAg prevalence 5.7%), three from Syria (1.0%), and one from Afghanistan (1.4%).

7.3.6 International developments

The European Centre for Disease Prevention and Control (ECDC) conducted a systematic review of chronic HBV prevalence in the European Union (EU) and Economic Area (EEA) countries based on studies published between 2005-2015. The overall HBV prevalence in the general population of the EU/EEA is estimated to be 0.9% (95% CI 0.7-1.2), corresponding to almost 4.7 million HBsAg-positive cases [4]. Among three at-risk populations: people in prison, MSM, and people who inject drugs (PWID), the highest HBsAg prevalence was found among people in prison (range of 0.3% - 25.2%) followed by PWID (0.5% - 6.1%) and MSM (0.0% - 1.4%) [5].

In Bavaria, Germany, mandatory screening for hepatitis B of asylum seekers is in place. A study describing the results of screening almost 95,000 asylum seekers in 2015 reports a prevalence of chronic HBV infection of 3.3% [6]. The HBsAg prevalence was highest in asylum seekers from Sierra Leone, Senegal and Mali, ranging between 15% and 18%. The prevalence in asylum seekers from the main countries of origin in Germany (and also in the Netherlands), Syria, Eritrea, Iraq and Afghanistan, were 1.7%, 4.9%, 1.0% and 3.9%, respectively.

7.3.7 Literature

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* RIVM publication

7.4 Human papillomavirus (HPV)

J. Hoes, T.M. Schurink-van 't Klooster, A.J. King, P.J. Woestenberg, P. van der Weele, H. Pasmans, A.W.M. Suijkerbuijk, J.A. Bogaards, V. Qendri, F.R.M. van der Klis, H.E. de Melker

7.4.1 Key points

- In 2017, incidence of cervical cancer cases increased while the number of deaths slightly decreased.
- In a prospective cohort study (HAVANA), high vaccine effectiveness (VE) against vaccine types HPV16/18 was found for persistent infections up to seven years post-vaccination (94.7%). In addition, significant cross-protection against persistent HPV infections by HPV31/45 was observed (75.4%).
- In a retrospective cohort study, no evidence was found for an increased risk of fatigue syndromes following HPV-vaccination. In 2015, the HPV16/18 prevalence among young STI clinic visitors declined from 23% pre-vaccination (2009) to 15% among women, and from 17% pre-vaccination to 11% among heterosexual men (PASSYON study).
- Whole genome sequencing on HPV16 and HPV18 positive genital swabs revealed a large population of unique whole genome HPV16/18 variants. In persisting HPV16/18 infections, strong conservation of the virus within hosts was observed.

7.4.2 Tables and figures

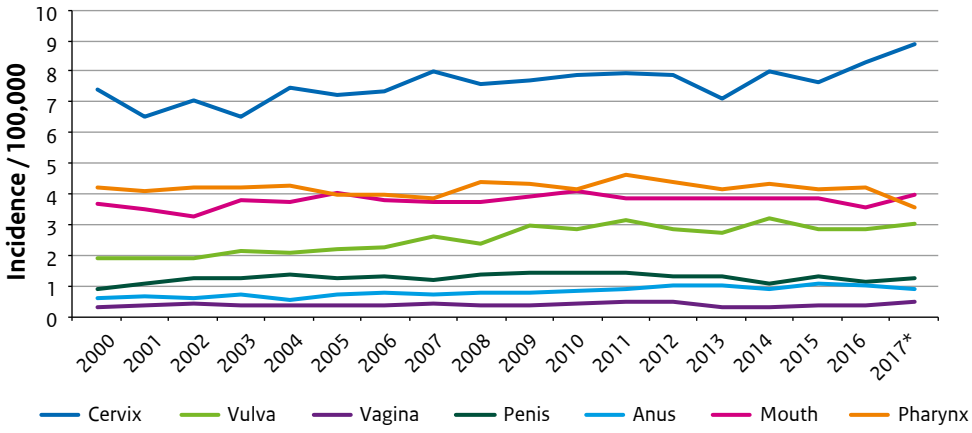

Figure 7.4.1 Incidence / 100,000 (standardised by the European standardised rate) of new cervical, anogenital, mouth/oral and pharynx/pharyngeal cancer cases in the Netherlands in the period 2000-2017, by cancer type

* Preliminary figures

Source: the Netherlands Cancer Registry (NKR)

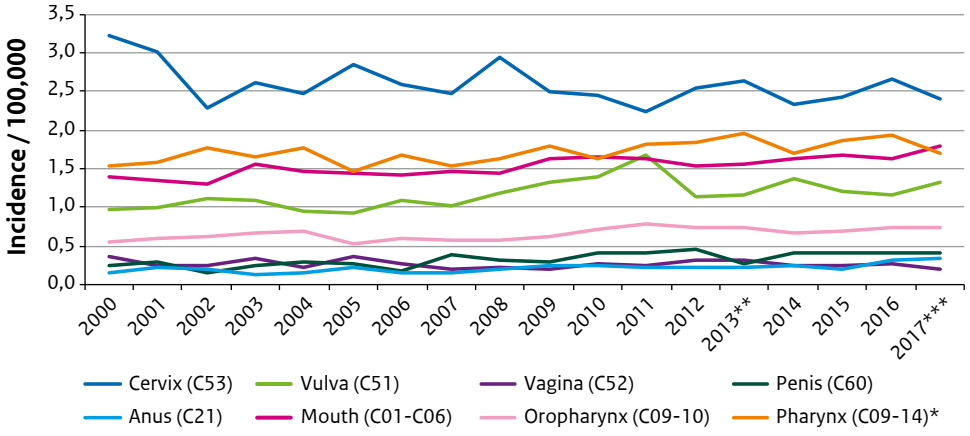

Figure 7.4.2 Incidence / 100,000 of deaths related to cervical, anogenital, mouth, oropharynx and pharynx cancer cases in the Netherlands in the period 2000-2017, by cancer type

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

** In 2013, CBS started to use international software for automatically coding the causes of death, making the number more reproducible and internationally comparable. Due to this change, some significant shifts can be seen in the causes of death.

*** Preliminary figures

Source: CBS

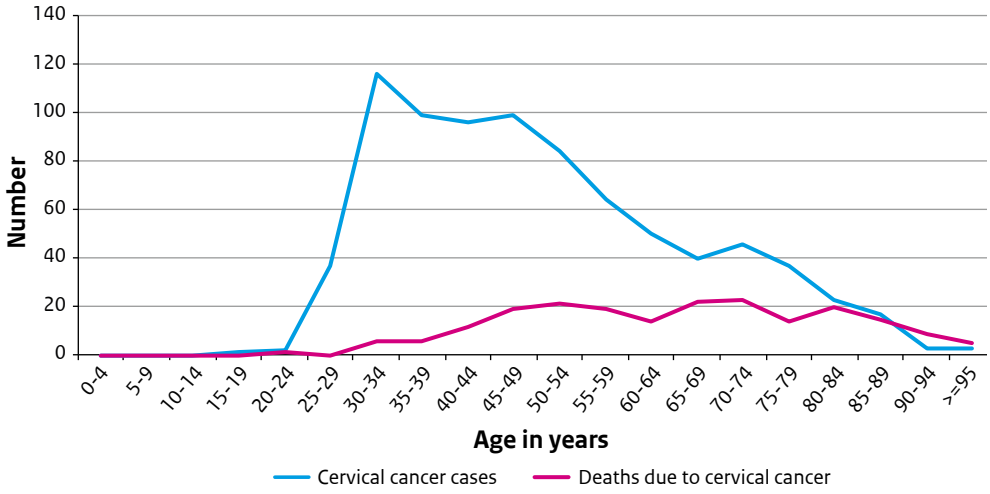

Figure 7.4.3 Age-specific number of cervical cancer cases and deaths due to cervical cancer in the Netherlands in 2017*

* Preliminary data

Table 7.4.1 Vaccine effectiveness against incident and persistent HPV infections in young women in the HAVANA study up to seven years post vaccination.

Incident infections	Adjusted* VE (95% CI)
Vaccine types (HPV16/18)	76.6% (64.5-84.5%)
Cross protective types (HPV31/45)	73.5% (56.2-84.0%)
Vaccine and cross protectives types (HPV16/18/31/45)	71.9% (61.1-79.7%)
Types 9-valent vaccine (HPV6/11/16/18/31/33/45/52/58)	31.7% (18.8-42.6%)
Persistent infections (12 months)	**Adjusted* VE (95% CI)**
Vaccine types (HPV16/18)	94.7% (82.8-98.3%)
Cross protective types (HPV31/45)	75.4% (39.3-90.0%)
Vaccine and cross protectives types (HPV16/18/31/45)	87.6% (75.1-93.9%)
Types 9-valent vaccine (HPV6/11/16/18/31/33/45/52/58)	46.9% (27.5-61.2%)

*Adjusted for age, urbanisation degree, ever smoked, ever had sexual intercourse, ever used contraception.

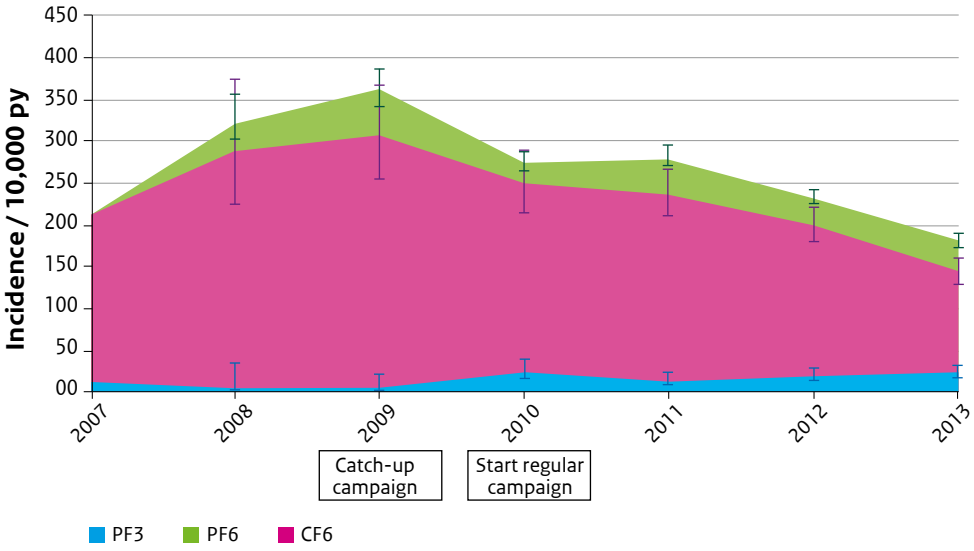

Figure 7.4.4 Incidences of certain and possible fatigue ³6 months and 3–6 months per year for 12–16-year-old girls

PY = person years, CF6 = certain fatigue ³6 months, PF6 = possible and certain fatigue ³6 months, PF3 = possible and certain fatigue 3–6 months

Table 7.4.2 Pre- and post-vaccination period incidences of long-term fatigue for 12–16-year-old girls

Criteria	Pre-vaccination period (2007-2008)			Post-vaccination period (2009-2013)			Adjusted IRR^ post vs. pre (95% CI)
	N events (%)	PY	Incidence / 10,000 PY (95% CI)	N events (%)	PY	Incidence / 10,000 PY (95% CI)	
CFS	1 (0.03)	2,758	3.6 (0.5-25.7)	5 (0.01)	57,214	0.9 (0.4-2.1)	0.24 (0.03-2.09)
CF6	2 (0.05)	2,758	7.3 (1.8-29.0)	111 (0.17)	57,092	19.4 (16.1-23.4)	2.70 (0.67-10.9)
PF6	73 (1.91)	2,715	268.9 (213.7-338.2)	1117 (1.74)	55,286	202.0 (190.5-214.2)	0.76 (0.60-0.96)
CF3	0 (0.00)	2,759	0.0	95 (0.15)	57,101	16.6 (13.6-20.3)	NA
PF3	6 (0.16)	2,755	21.8 (9.8-48.5)	212 (0.32)	56,924	37.2 (32.6-42.6)	1.72 (0.76-3.87)

^Adjusted for age

PY = person years, CI = confidence interval, CFS = chronic fatigue syndrome, CF6 = certain fatigue ³6 months, PF6 = possible and certain fatigue ³6 months, CF3 = certain fatigue 3-6 months, PF3 = possible and certain fatigue 3–6 months, IRR = incidence rate ratio

7.4.3 Epidemiology

A persistent infection with a high-risk human papillomavirus (hrHPV) type is a necessary cause for the development of cervical cancer. HPV can also cause other cancer types to develop, including vaginal, vulvar, penile, anal, mouth/oral and oropharyngeal cancer. Globally, approximately 640,000 cancer cases are attributable to HPV annually [1] and an estimated 17.5% of all new cancer cases among women aged 20-39 is caused by cervical cancer [2].

From 2016 onwards, the incidence of cervical cancer in the Netherlands continued to increase to reach a level of 8.91 per 100,000 in 2017 (preliminary data), compared with 8.32 per 100,000 in 2016 (Figure 7.4.1). The number of deaths due to cervical cancer slightly decreased in 2017 to 2.39 per 100,000 (preliminary data), compared with 2.67 per 100,000 in 2016 (Figure 7.4.2). Incidences and deaths related to other HPV-associated cancers in the Netherlands have remained more or less stable over the last five years (Figure 7.4.1 and 7.4.2). Annually in the Netherlands, approximately 600-850 women are diagnosed with cervical cancer and around 200 women die due to the disease. The age-specific number of cervical cancer cases and deaths caused by cervical cancer in the Netherlands is shown in Figure 7.4.3.

The non-oncogenic, low-risk HPV (lrHPV) types 6 and 11 can cause genital warts (GW). In 2017, the number of GW diagnoses at sexual health centres (SHC) was 1619 [3]. The positivity rate of GW among heterosexual men has remained relatively stable since 2013, while the positivity rate continued to decline among men who have sex with men (MSM) and women. This decline

started in 2008. The number of diagnoses of GW by general practitioners (GPs) was estimated at 37,500 in 2016, comparable to figures for the previous three years.

7.4.4 Current/ongoing research

7.4.4.1 Whole genome sequencing analysis of HPV16 and HPV18

Our recent whole genome sequencing studies on HPV16 and HPV18 positive genital swabs have led to new insights into the (intra-typic) diversity of HPV16 and HPV18 strains. These studies revealed a remarkably large population of unique whole genome HPV16/18 variants found to occur naturally in young women in the Netherlands [4, 5]. Unique variants of HPV16/18 are found in almost all women. In contrast, in women with persisting HPV16/18 infections, the same consensus sequence is found up to three years after baseline. This suggests strong conservation of the virus within hosts. Currently, limited information is available regarding the origins of this large diversity and how these sequence differences could affect infection outcome. The contrast of extremely high genetic diversity between hosts, yet strong conservation within hosts is not yet understood. With next-generation sequencing techniques becoming more accessible, it will be possible to perform ultra-deep sequencing which could detect minority variants within samples. This development could help us to investigate the relevance of within-host sequence variation. Ultra-deep sequencing on previously sequenced HPV16 positive genital swabs is ongoing. We expect these result will improve our understanding of the origins of this large diversity.

7.4.4.2 HPV amongst vaccinated and unvaccinated adolescents (HAVANA)

A prospective cohort study (HAVANA) initiated in 2009 among vaccinated and unvaccinated girls aged 14 - 16 eligible for the catch-up campaign, is still ongoing. The primary aim of this study is to monitor the effect of the bivalent HPV vaccination on HPV-type specific presence amongst vaccinated and unvaccinated young women. Vaginal self-swabs collected annually in this cohort were tested for the presence of HPV DNA. Seven years after vaccination, in both among vaccinated and unvaccinated participants, HPV51 and HPV52 were the most prevalent hrHPV types. Vaccine effectiveness (VE) against incident and persistent infections was determined. The bivalent vaccine showed a significantly high VE against both incident and 12-month persisting vaccine type infections (HPV16/18). In addition, high VE against cross protective types was observed (HPV31/45). The VE up to seven years post-vaccination against both incident and persistent infections is shown in Table 7.4.1.

In 2016, a second prospective cohort study was initiated among vaccinated and unvaccinated girls born in 2001 who were eligible for a two-dose schedule in 2014 (HAVANA2). Follow-up of this cohort is planned yearly for at least five years in which girls are asked to complete a questionnaire and hand in a vaginal self-swab. For the first round of this study, 39,261 girls were invited for participation. Of these, 2,036 handed in a vaginal self-swab in the first study round (54% vaccinated, 46% unvaccinated). The most prevalent hrHPV types were HPV16 and HPV51, although the absolute number of infections was low n=4 (all unvaccinated) and n=3 (two unvaccinated), respectively. In the second round conducted in September 2017, 1,857 swabs were received.

7.4.4.3 *Bivalent HPV vaccine leads to reduced (vaccine type) viral load in incident and persistent infections in young Dutch females*

We monitored the effects of vaccination with the bivalent HPV vaccine according to the three-dose schedule on the viral load of infections in vaccinated and non-vaccinated individuals. Study participants were recruited in a prospective cohort study (HAVANA), in which samples were obtained annually. Type-specific viral load (VL) assays were developed for HPV6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66. VL of incident clearing HPV16 ($p<0.05$) and HPV18 ($p<0.05$) infections was significantly lower in vaccinated individuals than in unvaccinated individuals. Cross-protection was observed against incident clearing (IR: 0.26, 95%CI: 0.11-0.61) and persistent (IR: 0.20, 95%CI: 0.08-0.53) HPV31 infections as also reported for this HAVANA study by Donken et al [6], but could not be associated with VL. In general, VL was lower in infections occurring in vaccinated than in non-vaccinated individuals, irrespective of HPV type.

7.4.4.4 *Trends in HPV16/18 positivity among female and heterosexual male STI clinic visitors (PASSYON study)*

Using data from the PASSYON study, a biennial cross-sectional survey among visitors to sexually transmitted infections (STI) clinics aged 16-24 [7], we studied trends in the prevalence of the vaccine-types HPV16/18 since the introduction of HPV vaccination in the Netherlands in 2009. Among all women, the HPV16/18 prevalence decreased from 23% pre-vaccination to 15% in 2015 (adjusted prevalence ratio 0.62 (95%CI 0.52-0.74)), related to the increased proportion of women who reported being vaccinated (2.3% in 2009 and 37% in 2015). Among heterosexual men, the HPV16/18 prevalence decreased from 17% pre-vaccination to 11% in 2015 (adjusted prevalence ratio 0.52 (95%CI 0.36-0.75)). Among unvaccinated women, the HPV16/18 prevalence in 2015 was not different from pre-vaccination. These results suggest that heterosexual men benefit from herd-protection from girls-only vaccination, however herd effects were not observed among unvaccinated women up to 6 years post vaccination.

7.4.4.5 *HPV (sero)prevalence among young MSM visiting the STI clinic (PASSYON study)*

MSM are disproportionally affected by HPV-related cancers, especially anal cancer. However, MSM are expected to benefit less from herd protection from girls-only HPV vaccination. To study if targeted HPV vaccination for MSM could be beneficial, we assessed the prevalence of vaccine-preventable HPV types among MSM aged 16 – 24 visiting STI clinics, using data from the PASSYON study.

Among the 447 MSM included, no trends in penile or anal HPV prevalence over time were seen, except for anal HPV18 that declined from 15% in 2009 to 3.8% in 2015 (p trend<0.01). In total, 80%, 63% and 53% were penile and anal HPV DNA negative for HPV16/18, HPV6/11/16/18 and HPV6/11/16/18/31/33/45/52/58 respectively, and 66% and 46% were HPV DNA negative and seronegative for HPV16/18 and HPV16/18/31/33/45/52/58 respectively. Because the majority of young MSM visiting STI clinics were (sero)negative for HPV16/18, the most important oncogenic types in males, targeting this group for HPV vaccination may be beneficial.

7.4.4.6 Monitoring the immunogenicity of the two-dose schedule (HPV-2D)

To monitor the effects of the change from a three-dose to a two-dose schedule on immunogenicity, a cohort study among girls who received a two-dose schedule was initiated in 2014. Annually, girls born in 2001 fill in a questionnaire and supply a blood sample to assess the quantity and quality of the immune response.
Results after 24 months of follow-up show high antibody levels, with high avidity (>75%), against vaccine-types HPV16/18, despite a decline in levels over two years [8]. The high antibody avidity remained stable for up to 24 months. Antibody levels and avidity were considerably lower for cross-protective types (HPV 31, 33, 45, 52, 58), with a somewhat higher level of waning for up to 24 months.

7.4.4.7 Monitoring the immunogenicity of a one-dose schedule (HPV-1D)

A cross-sectional study was conducted in 2017 to monitor the immunogenicity of one-dose bivalent HPV vaccinated girls in the Netherlands. From 464 girls born between 1998 and 2003 who received one, two, or three doses of the HPV vaccine between 2011-2016, we received a questionnaire and a bloodspot card to analyse HPV16/18/31/33/45/52/58 and HPV6/11 antibody concentrations in a one dose versus a two or three-dose schedule. In addition, 206 of these 464 girls visited one of our consultation hours for a venepuncture for additional blood samples, in order to perform in depth immune cell analyses.
The one dose schedule is immunogenic and induces long-term antibody responses and HPV-specific T- and B-cell memory. However, 63% of the 1D vaccinated girls stay below 100LU/mL which is not seen in 2D and 3D vaccinated girls. Moreover, some of the 1D vaccinated girls do not show HPV-specific B- and T cells.

7.4.4.8 Safety

An extensive description of the signals and international developments regarding safety aspects of HPV vaccination is included in Chapter 5. In 2013, Lareb published an overview of reports of long-lasting fatigue following bivalent HPV-vaccination. After an update of this overview in 2015, concerns regarding the safety of this vaccine were picked up by the media which led to further reports of long-lasting fatigue. Therefore, the RIVM investigated a possible association between HPV-vaccination and long-term fatigue. In this retrospective cohort study conducted in the Integrated Primary Care Information (IPCI) database, we investigated the occurrence of chronic fatigue syndrome (CFS), fatigue >=6 months and 3-6 months in the cohort of girls born in 1991-2000 in the years 2007-2014 (2007-2008 pre-vaccination and 2009-2014 post-vaccination). Patients with certain fatigue >=6m were asked for consent to link their primary care information with vaccination data.
The cohort consisted of 69,429 12-16-year-old girls accounting for 2,758 person years (PY) pre-vaccination and 57,214 PY post-vaccination. Fatigue >=6m and 3-6m was frequently found among adolescent girls, but CFS was rarely diagnosed. No statistically significant increased incidence rates were found post-vaccination compared to similar age groups of girls pre-vaccination (Figure 7.4.4, Table 7.4.2). A self-controlled case series (SCCS) analysis in 16 consenting vaccinated cases revealed no elevated risk of certain fatigue >=6m in the high-risk period of 12 months after vaccination (crude RR: 0.51 (95%CI 0.11-2.41); age-adjusted RR: 0.62 (0.07-5.49). We found no evidence for an increased risk of fatigue syndromes following HPV-vaccination [9].

7.4.4.9 *Modelling*

Vaccinating boys in addition to girls is an appealing complementary strategy for the prevention of HPV-related diseases, especially at moderate vaccine uptake among girls [10]. Sex-neutral vaccination against HPV is advocated on several grounds; equity, bolstering of herd effects to women, direct benefit for vaccinated boys, and protection of MSM. We delineated the incremental benefit of vaccinating boys along with girls in terms of HPV16/18-related cancer prevention among women, heterosexual men and MSM. Boys' vaccination produced most health gains through indirect cervical cancer prevention at ≤80% vaccine uptake in girls, assuming uptake among boys to be less than or equal to girls. At ≥90% vaccine uptake in girls, the incremental gain from vaccinating boys was mostly due to anal cancer prevention among MSM [11]. This supports the notion that boys' vaccination against HPV can be considered for different reasons, depending on the established vaccine uptake in girl-only programmes. Furthermore, vaccinating boys in addition to girls is only modestly less efficient than increasing uptake among girls, and it is highly likely to be cost-effective in European tender-based settings [12], including the Netherlands [13].

In the UK, the JCVI (Joint Committee on Vaccination and Immunisation) recommended offering HPV vaccine to MSM aged ≤45 years at genitourinary medicine and HIV clinics. The Committee's advice followed favourable cost-effectiveness analyses for selective MSM vaccination with quadrivalent HPV vaccine in England [14]. We explored the potential effectiveness of targeted vaccination in reducing anogenital HPV16 transmission among MSM in the Netherlands. HPV16 causes the majority of HPV-related cancers in males and is included in all registered HPV vaccines. We assumed 85% efficacy against future HPV16 infections and age-specific uptake rates similar to hepatitis B vaccination among MSM in the Netherlands. Targeted vaccination was contrasted with vaccination of 12-year-old boys at 40% uptake annually. Based on predictions from a range of penile-anal HPV16 transmission models, we estimated that around 30% of anogenital infections might be prevented if uptake similar to hepatitis B vaccine among MSM throughout the Netherlands were to be realised. The predicted reductions improved to around 50% if uptake rates throughout the Netherlands were doubled relative to hepatitis B vaccination. The reductions in HPV16 infection prevalence were mostly achieved within 30 years of a targeted immunisation campaign, during which they exceeded those induced by vaccination of preadolescents, if started simultaneously. In conclusion, targeted vaccination may generate considerable reductions in anogenital HPV16 infections among MSM, and has the potential to accelerate anal cancer prevention compared to sex-neutral vaccination in preadolescence.

7.4.5 International developments

7.4.5.1 *Impact of HPV vaccination*

To date, over 80 countries have implemented HPV vaccination in their NIP for girls, mostly targeting 12/13-year-olds [15]. All three licensed vaccines are in use and an increasing number of countries are supplying the HPV vaccine to boys [16].

Two sub-studies from Sweden showed a declining proportion of quadrivalent vaccine type HPV infections. The proportion (4%) of the vaccine-type HPV in a population of 18-year-old

vaccine eligible girls was significantly lower than the proportion in another sub-study on outpatients (<26 years old) in the pre-vaccine era (25.7%). The proportion of the high-risk vaccine-type HPV16/18 declined by 59% (P=0.0048) in the outpatients in the post-vaccine period (8.7%) compared to the pre-vaccine era (21.0%), although the decline was only observed among those aged less than 26 years [17]. In Sweden, a significant reduction in GW incidence was observed six years after vaccine implementation [18]. The average annual percent changes (AAPC) in incidence for women aged 15–24 showed a declining trend from 2008 onwards (AACP-range: −8.5% to −18.5%). In men aged 15-29, a one-year delay in in this decline was observed (AACP-range: −7.0% to −16.6% from 2010 onwards).

In the long term follow-up study (LTFU) (a study following women from Denmark, Iceland, Norway, and Sweden initially included in the FUTURE II clinical trial on quadrivalent HPV vaccine), VE against cervical intraepithelial neoplasia (CIN2, CIN3), adenocarcinoma in situ (AIS), and cervical cancer related to HPV16/18 were monitored. Observed incidence was compared to expected incidence in an unvaccinated cohort, showing VE against CIN2 or worse of at least 90% up to ten years post-vaccination [19].

A cross-sectional study from the US showed a significant effect of having received at least one dose of HPV vaccine on the prevalence of oral HPV type 6/11/16/18. An estimated 88.2% (95%CI, 5.7-98.5) reduction in prevalence was shown for vaccinated individuals aged 18-33. However, the population-level effect was modest due to low vaccine uptake [20].

Machalek and colleagues (Australia) showed a significant reduction in quadrivalent HPV vaccine type prevalence in women aged 18-35 in 2015 compared to 2005 (nine years after vaccination implementation) [21]. HPV prevalence decreased from 22.7% (2005–2007) to 1.5% (2015) (P trend <0.001) among women aged 18–24, and from 11.8% (2005-2007) to 1.1% (2015) (p = 0.001) among 25-35-year-old women. The decline in the older age group is indicative of herd protection.

In Finland, participants (16-17 year-olds) to Patricia and HPV-012 (clinical trials for the bivalent HPV vaccine) were compared to non-vaccinated women (18-19 year-olds) in a passive registry-based follow-up. Based on the Finish Cancer Registry, vaccine efficacy of 66% for HPV-16/18 vaccine against any CIN3 and invasive cervical cancer ten years post vaccination was found [22]. Vaccine efficacy was not observed in vaccinated participants who were HPV16 DNA positive at baseline.

Furthermore, in a register based cohort study in Denmark, a significant reduction in high-grade squamous intraepithelial lesion (HSIL) was observed following quadrivalent HPV vaccination. In this study, the results after first cervical screening at age 23 between an HPV-vaccinated and an unvaccinated birth cohort (1993 and 1983, respectively) were compared. Detection of HSIL was significantly lower in the 1993 than in the 1983 cohort, RR = 0.6 (95% CI 0.5-0.7), p <0.0001, while the opposite pattern was seen for atypical squamous cell of undetermined significance and worse (ASCUS) RR = 1.4 (95% CI 1.2–1.6), p <0.0001 [23].

In 2018, a Cochrache review on HPV vaccination was published in order to evaluate the harms and protection of the vaccine against cervical precancer. Trials on safety and efficacy were included (n=26) with a focus on women under 26 years of age. The authors concluded that "there is high-certainty evidence that HPV vaccines protect against cervical precancer in adolescent girls and young women aged 15 to 26". The observed effect was higher for lesions associated with HPV16/18 and for women who were hrHPV negative at baseline. No increased risk of serious adverse events was found [24]. However, the review raised criticism as well; it was stated that not all eligible trials were included, possibly introducing reporting bias, and that the review was influenced by biased trial designs. Authors should have attempted to identify all trials and their limitations more accurately. Therefore, this review could not be considered 'Trusted Evidence' according to the critics [25]. The International Cochrane Collaboration responded to these critics and stated among other that the Cochrane Review did not miss "nearly half of the eligible trials" [26].

7.4.5.2 One dose schedule

A multi-centered randomised trial of two versus three doses of quadrivalent HPV vaccination (Gardasil) in girls aged 10-18 in India, indicated 28% of the participants only received one dose [27, 28]. These one dose recipients showed robust and sustained antibody levels against HPV16 and HPV18, stable over a 4 year period. Although being inferior to two- and three-dose vaccinated girls, frequencies of incident and persistent HPV16 and HPV18 infections were similar and uniformly low in all the different doses groups up to 7 years of follow-up.
In another large randomised clinical, the Costa Rica Vaccine Trial, 20% of the vaccinated girls received only one-dose of the bivalent HPV vaccine (Cervarix). Antibody levels after one-dose showed to be up to 9-times higher than the levels elicited after natural infection. Moreover, these levels remained constant for up to 7 years [29].

These data indicate that a single dose of the quadrivalent or bivalent HPV vaccine is immunogenic, which might indicate a lasting protection against infections with HPV16 and / or HPV18. Significant and long-lasting protective effect of a single dose can be a strong argument to introduce one dose of the HPV vaccine in many low income countries where the current standard of care for cervical cancer prevention is 'no intervention'. However, it has to noted that the group of recipients that received only one-dose is relatively small.

7.4.5.3 Male vaccination

Following Austria, Liechtenstein and Switzerland (and Australia, New-Zealand, Canada, USA, Brazil and Argentina outside Europe), the governments of Norway, Sweden and Italy have also decided to allow both boys and girls to be vaccinated against HPV following advice that sex-neutral vaccination in preadolescence makes health economic sense [30-32]. In Germany, reimbursement of vaccine costs to boys has been recommended on a regional level, but has been deemed not cost-effective in a formal cost-effectiveness study [33]. Likewise, the JCVI advised against sex-neutral vaccination in preadolescence in the UK, arguing that the currently relatively high vaccine uptake by girls (about 85%) provides enough herd protection to make it cost-ineffective to vaccinate boys. However, most economic analyses, while acknowledging the critical role of vaccine coverage in cost-effectiveness calculations, have neglected to

account for cost reductions owing to HPV vaccine procurement [34]. To better understand policy differences between European countries, a closer look at the price of the HPV vaccines in NIPs is required, given its key role in the health economic evaluations of HPV vaccination. A systematic review of procurement notices and awards for the HPV vaccines from the online platform for public procurement in Europe (published from January 2007 until January 2018), revealed that the average price per dose for the first generation HPV vaccines in tender-based settings decreased two to four-fold compared to market introductory prices. HPV vaccine procurement is thus an efficient cost-containment strategy.

7.4.5.4 *Nonavalent vaccine*

Final analyses of a randomised, double-blind 9-valent HPV vaccine trial among 16-26 year-old women have documented sustained antibody responses and high efficacy for up to 6 years following first dose administration [35]. In a multi-centre study involving 105 study sites in 18 countries, over 14,000 participants were randomly assigned to receive 9-valent or quadrivalent HPV vaccine. In per-protocol analyses, the efficacy against high-grade cervical, vulvar and vaginal disease related to HPV types 31, 33, 45, 52, and 58 (i.e. types not covered by the quadrivalent vaccine) was 97.4% (95%CI 85.0-99.9%). Geometric mean antibody titers against HPV 6, 11, 16, and 18 were non-inferior in the 9valent versus quadrivalent HPV vaccine group from month 1 to 3 years after vaccination. No clinically meaningful differences in serious adverse events were noted between the study groups. A combined analysis of 7 phase III trials concluded that the 9-valent HPV vaccine was generally well tolerated in subjects aged 9 to 26, although injection-site adverse events were more common with 9-valent compared to quadrivalent HPV vaccine [36]. Efficacy results in young women were extrapolated to preadolescent and young adolescent girls and boys and to young men by demonstration of non-inferior immunogenicity in these groups versus young women [37]. Only one study investigated a 2-dose schedule with 9-valent HPV vaccine, demonstrating that immunogenicity following a 2dose immunisation schedule among 9-14 year-old girls and boys was not inferior to a 3-dose schedule in 16-26 year-old women [38]. This evidence was considered of sufficiently good quality to recommend 2-dose 9-valent HPV vaccination in immunocompetent populations [39].

7.4.5.5 *Cost-effectiveness*

The cost-effectiveness of the bivalent and quadrivalent HPV vaccination in addition, we assessed the current cervical cancer screening programme in Germany [33]. In the base case analysis, the cost-effectiveness of vaccinating 12-year-old girls with a 3-dose schedule was evaluated. In a scenario analysis, the use of a 2-dose schedule and vaccinating boys was also included. Incremental Cost-Effectiveness Ratios (ICER) of a 3-dose schedule in girls were €34,249 per quality-adjusted life year (QALY) gained for the bivalent and €14,711 per QALY gained for the quadrivalent vaccine. Inclusion of productivity losses, that is adopting a societal perspective, decreased ICERs by up to 40%. From a societal perspective, a 2-dose approach using the quadrivalent vaccine was a cost-saving strategy, while using the bivalent vaccine resulted in an ICER of €13,248 per QALY gained.
Irrespective of the perspective adopted, and including a two-dose vaccination scheme, additional vaccination of boys resulted in ICERs exceeding €50,000 per QALY at a vaccine

coverage of 50% in girls. In this study, other cancers than cervical were not included. Including the impact on vaginal, vulvar, penile, anal, and head and neck cancer would improve the cost-effectiveness of HPV vaccination.

In a cost-effectiveness analysis for the Italian setting, two strategies with the nine-valent vaccine (cervical cancer screening and vaccination in girls only or vaccination in boys and girls) were compared to four alternative strategies (cervical cancer screening and vaccination with the current quadrivalent vaccine in girls only, in both boys and girls, with bivalent vaccine in girls, and screening strategy only) [40]. The nine-valent vaccine in a programme including girls and boys would further reduce the incidence of cervical cancer, anal cancer, and genital warts avoided after 100 years. Comparing the nine-valent vaccine to the quadrivalent vaccine, the ICER was €10,463 per QALY gained for universal vaccination and €4483 for girl-only vaccination.

The cost-effectiveness of a targeted HPV vaccination programme for young (15–26) MSM compared to no vaccination and the current boys' vaccination programme was assessed for Australia [41]. The model predicted that a vaccination programme for boys only with a coverage of at least 84% would achieve a reduction of 90% in HPV infection in MSM, similar to what has occurred in women with a girls only vaccine programme. The addition of a targeted catch-up programme for young MSM to the boys' programme would enable this to be achieved 2–3 years earlier and be highly cost effective, only if implemented soon after commencement of the boys' programme. The ICER ranged from $AU 6645 for 5% vaccination additions to $AU 6788 for 20% vaccination additions per QALY gained.

7.4.5.6 Screening uptake

A retrospective cohort study in the USA examined screening initiation among women reaching 21 years of age and adherence to screening intervals among women 25-30 years of age in a large health care delivery system. In comparison with unvaccinated women, adjusted hazard ratios for screening initiation among women who had been vaccinated against HPV were 1.19 (95%CI, 1.11-1.28), 1.44 (95%CI, 1.34-1.53), and 1.57 (95%CI, 1.50-1.65) for 1, 2, and 3 doses, respectively. Adjusted odds ratios for screening interval adherence were 0.93 (95%CI, 0.83-1.04), 1.73 (95%CI, 1.52-1.97), and 2.29 (95%CI, 2.05-2.56), for 1, 2, and 3 doses, respectively [42]. This study indicates the need for improving efforts to initiate screening among women who did not receive an HPV vaccination.

7.4.6 Literature

7.4.6.1 References

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7.5 Measles

T. Woudenberg, R. van Binnendijk, R. Bodewes, W.L.M. Ruijs, I. Brinkman, N.Y. Rots, C.A.C.M. van Els, I.K. Veldhuijzen

7.5.1 Key points

- With 16 reported cases in 2017, the number of measles cases was low, but higher than the previous two years.
- In the first six months of 2018, 17 cases were reported of which five in children were too young to be vaccinated.
- Genotypes B3 and D8 were detected; the two genotypes most frequently detected in other European countries.

7.5.2 Tables and figures

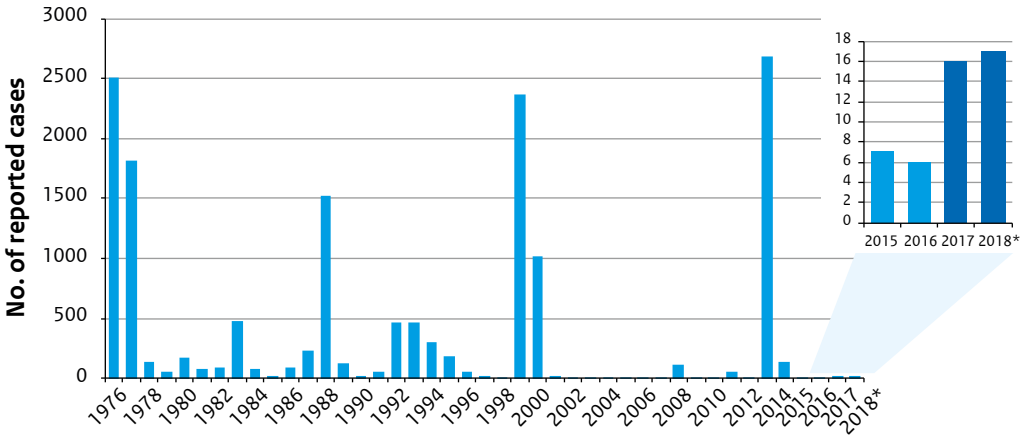

Figure 7.5.1 Annual reported measles cases since the introduction of measles in the Dutch vaccination programme.

* up to July

7.5.3 Epidemiology

In 2017, 16 cases were reported (Figure 7.5.1). The mean age was 28 years (range 2-58 years). Six cases were imported with measles acquired in Spain (n=2), Germany, Somalia (n=2) and Ivory Coast. One of these patients resulted in a cluster with three secondary infections. Five other patients were infected in the Netherlands from an unknown source. Two of these led to small clusters, with one secondary infection each.

The majority of cases were unvaccinated (n=12) and the vaccination status was unknown for one. Three cases were reportedly vaccinated, although one only once, and the vaccination status could not be verified for the other two vaccinated cases. Seven cases (all unvaccinated) were hospitalised, one of them was a two year old with pneumonia.

In the first six months of 2018, 17 cases were reported; 5 clusters with 14 patients in total and three solitary cases. The mean age was 19 years (range 0-50 years). Four patients acquired the infection abroad, two in Romania, one in Portugal, and one in Greece. These imported cases led to three clusters with four secondary infections. Another four patients had no travel history and the source of infection remained unknown. Two of these cases led to clusters with two and three secondary infections.

While in 2015-2017 no cases were reported in children below the age of two years, in the first half of 2018, five cases occurred in children aged under 14 months who were too young to be vaccinated. Two of them contracted measles on holiday in Portugal and while visiting family in Romania. The other three children were infected in the Netherlands through contact with a family member with measles (n=2) or through an unknown source. Of the other 12 patients, six were unvaccinated, three incompletely vaccinated, one completely vaccinated, and the vaccination status for two was unknown. All five children who were too young to be vaccinated were hospitalised with respiratory problems and/or dehydration. Five other patients were hospitalised, of whom four were unvaccinated and one was vaccinated once. The measles infection in the twice vaccinated person was a clinically mild secondary infection in a health care worker.

7.5.4 Pathogen

A genotype was determined for the detected measles virus of 13 reported cases in 2017, and for 14 reported cases in the first six months of 2018. In 2017, measles virus genotype D8 was detected in 10 cases (77%) and measles virus genotype B3 was detected in three cases (23%). In 2018, measles virus genotype B3 was detected in 12 cases (86%) and measles virus genotype D8 was detected in two cases (14%). In 2017 and 2018, measles viruses of genotypes B3 and D8 were also the most detected two genotypes in Europe (and other parts of the world) based on sequence data available in the global Measles Nucleotide Surveillance (MeaNS) database [1]. In most measles virus cases in the Netherlands in 2017/2018, the nucleotide sequence data obtained from measles viruses supported the epidemiological data about a possible origin of infection, or provided additional information about a possible link to measles virus cases in other countries for which recent measles virus nucleotide sequence data was available in the MeaNS database.

7.5.5 Research

7.5.5.1 The reduction of measles transmission during school vacations

The Dutch 2013-2014 measles epidemic showed a large reduction in measles incidence during the summer vacation, followed by a resurgence. The data of the epidemic were used to estimate the impact of the school vacations on the epidemic, by use of a measles transmission model [2]. It turned out that contact rates had been reduced by 53%, and that almost 5,000

cases had been averted as a result of the summer vacation. It was also concluded that measles transmissibility had not changed since the start of mass vaccination.

7.5.5.2 *Risk factors for persisting measles susceptibility: a case-control study among unvaccinated orthodox Protestants*

During the measles outbreak of 2013-2014, 17% of the reported cases were over 14 years old. Apparently, they were not infected during the 1999-2000 outbreak, 13 years earlier. A case-control study among unvaccinated orthodox Protestants was carried out to identify risk factors for this so-called persisting measles susceptibility culminating in measles infections at an older age with an increased risk of complications [3]. Risk factors for persisting measles susceptibility for infants/toddlers in 1999/2000 were associated with a moderately conservative church, absence of older siblings, and residency outside low vaccination coverage (LVC)-municipalities. Risk factors for primary school-aged children were residency outside LVC-municipalities and attendance of non-orthodox Protestant primary school.

7.5.5.3 *Seroepidemiological study among asylum seekers*

We conducted a seroprevalence study among refugees aged 18 to 45 years to assess the level of protection against nine vaccine preventable diseases. In 2016, over 600 refugees from Syria, Afghanistan, Iraq, Iran and Eritrea living in three large asylum seeker centres participated in the study [4]. The overall seroprevalence was high at 88%, but under the WHO elimination goal of 95%. The range between countries was 83%-93%. Seroprevalence was highest among participants from Eritrea. The lowest seroprevalence was observed for participants from Iran; overall 83.5% and for those aged 18-25 years (69.7%). Even though adult asylum seekers are less well protected against measles than the Dutch population (96%), it is not considered necessary to change the vaccination policy, as the level of protection in the general population is high. The lower prevalence particularly in the youngest age group (18-25) stresses the importance of adhering to the current policy of assessing the vaccination status of asylum seekers aged under 18 and offering vaccination according to the NIP.

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

Children who received an early measles immunisation between 6-12 months during the latest measles epidemic were followed up to the age of 4 to measure the effect on antibody responses and immune protection. Especially those children vaccinated when younger than 9 months have lower neutralizing antibody concentrations compared to infants vaccinated at a later age, despite an additional vaccination at 14 months. This may result in an increased number of children susceptible to measles in the long-term.

7.5.6 International developments

In 2017, the EU experienced a resurgence of measles, with several outbreaks and 37 fatalities [5]. In total, 21,315 measles cases were reported from 28 European countries. Most were reported from Romania (5608), Italy (5098), and Greece (967). Adults aged above 20 and children aged under 5 were most affected, with an incidence of 365.9 and 164.4 cases per million population respectively. In 2018, the resurgence of measles continued, with large outbreaks in several European countries [6]. Romania reported 3,284 cases including 19 deaths

up to 11 May, Greece reported 2,097 cases including two deaths, and France reported 2,306 cases in the period up to 27 May 2018. Measles transmission has also been observed in countries aligning Europe such as Servia and Ukraine, with 5,402 and 18,144 reported cases, respectively, as of 29 May.

7.5.7 Literature

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* RIVM publication

7.6 Meningococcal disease

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7.6.1 Key points

- The number of cases with meningococcal serogroup C disease is still very low, with only nine cases reported in 2017.
- There is an ongoing increase in the number of cases with meningococcal serogroup W (MenW) disease caused by a hypervirulent clonal complex 11 strain, with 80 cases reported in 2017 and 78 up to August 2018.
- Because of this increase, the MenC vaccination given at 14 months has been replaced by a quadrivalent MenACWY vaccination since May 2018. As of October 2018, 13-14 year olds will be offered MenACWY vaccination. In 2019, there will be a catch-up campaign for all 15-18 year olds.
- MenW disease occurs across all age groups, with peaks in incidence in <2 year olds and 14-24 year olds, and increasing incidence with age from 45-50 years onwards.
- The case fatality of MenW disease from January 2015 to August 2018 was 17%, which is substantially higher than for other serogroups.
- In 2018 (up to August), the incidence of meningococcal serogroup B (MenB) disease was lower than for MenW disease, although in <5 year olds the incidence of MenB disease is still higher than for MenW disease, and has slightly increased since 2015.
- The number of cases of meningococcal disease caused by serogroup Y or other serogroups is low and stable.

7.6.2 Figures

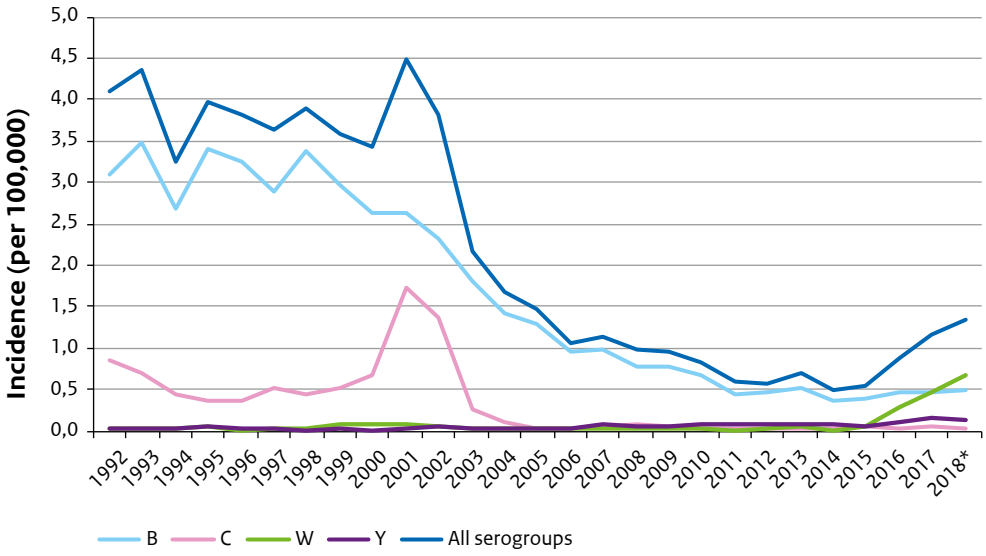

Figure 7.6.1 Incidence of meningococcal disease by serogroup, 1992-2018* (*up to August)
Source: NRLBM

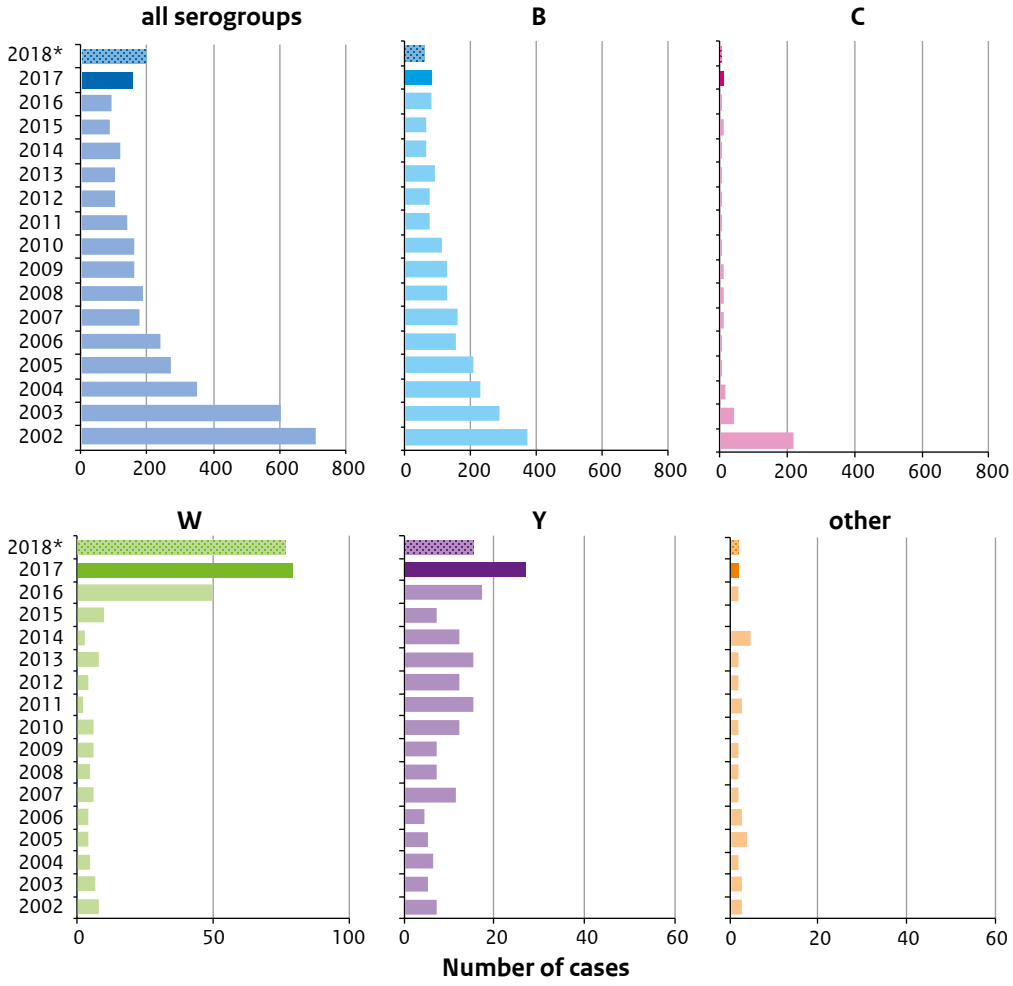

Figure 7.6.2 Number of cases of meningococcal disease by serogroup, 2002-2018* (*up to August)
Note the different scale for the upper and lower graphs
Source: NRLBM

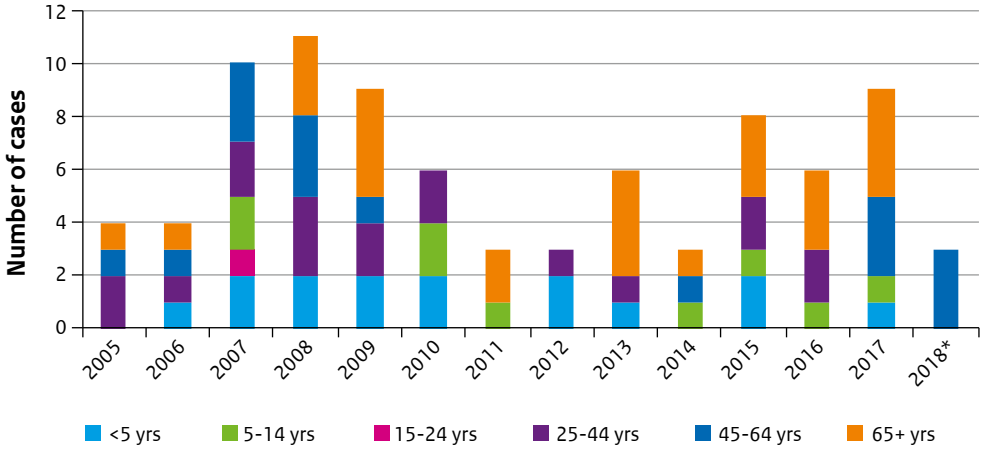

Figure 7.6.3 Number of cases of meningococcal serogroup C disease by age group, 2005-2018* (*up to August)
Source: NRLBM

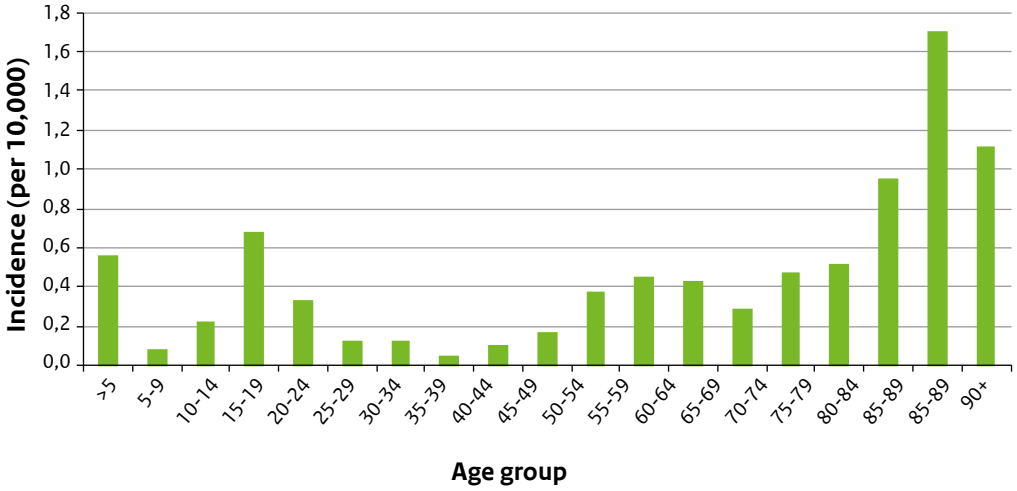

Figure 7.6.4 Age-specific incidence of meningococcal serogroup W disease, 2015-2018* (*up to August)
Source: NRLBM

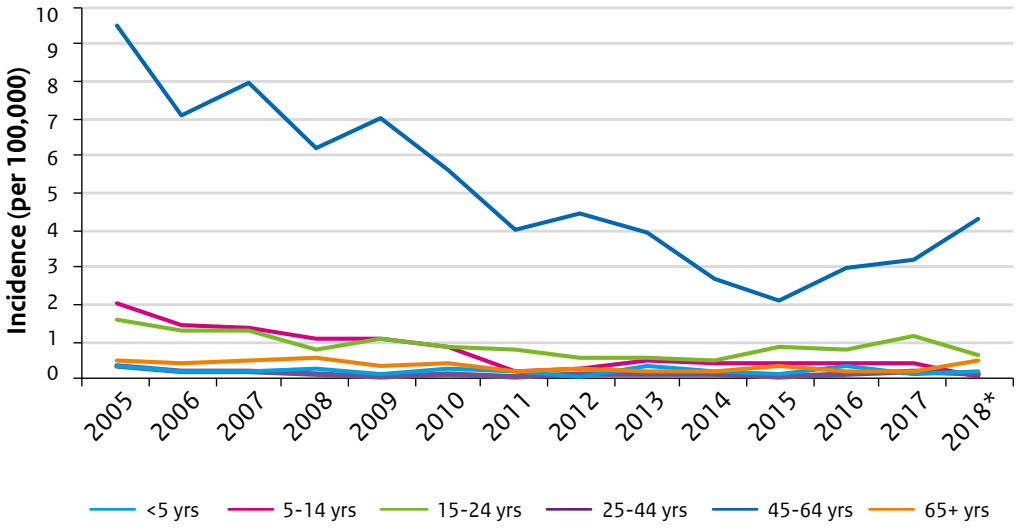

Figure 7.6.5 Age-specific incidence of meningococcal serogroup B disease, 2005-2018* (*up to August)

Source: NRLBM

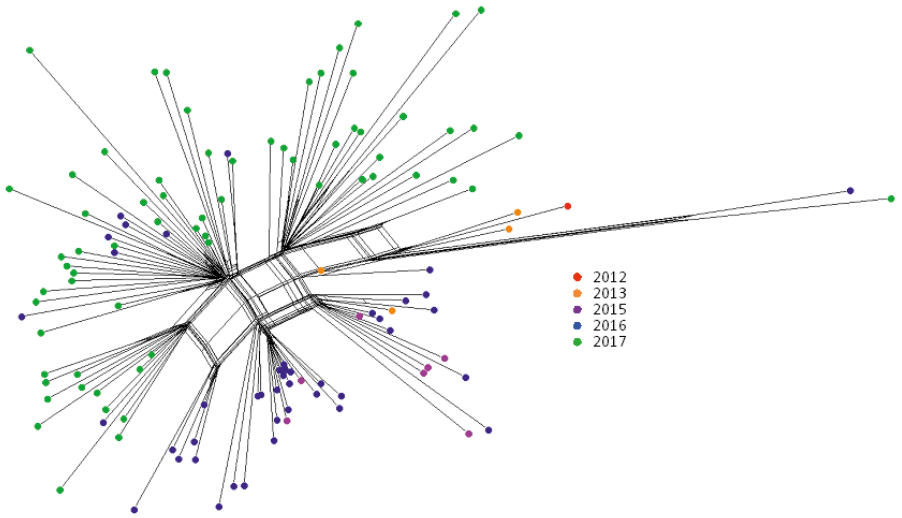

Figure 7.6.6 Neighbour-net phylogenetic network analysis of all available genomes of serogroup W clonal complex 11 isolates from the Netherlands, 2012–2017 (n = 121)

Colours represent the years when the isolates were obtained. Genomes were compared using the PubMLST genome comparator tool using core genome multilocus sequence typing (cgMLST v1.0) {Bratcher, 2014 #17}. The resulting distance matrices were visualised with SplitsTree4 version 4.13.1 {Huson, 1998 #16}.

Source: NRLBM

7.6.3 Epidemiology

7.6.3.1 Meningococcal disease

The incidence of meningococcal disease declined from 4.5 per 100,000 in 2001 to 0.49 per 100,000 in 2014, but increased from 2015 to an incidence of 1.3 per 100,000 in 2018 (data up to August) (Figure 7.6.1). This increase is mainly due to an ongoing increase of a serogroup W clonal complex 11 strain (see section 7.6.3.3).

7.6.3.2 Meningococcal serogroup C

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 number of cases of meningococcal serogroup C (MenC) disease has decreased enormously, from 277 in 2001 to on average 6 cases per year from 2005 (Figure 7.6.2). The incidence decreased in all age groups due to herd protection, and has been lower than 0.1 per 100,000 since 2005 (Figure 7.6.1).
In 2017, 5% of all meningococcal cases were serogroup C. Nine cases of MenC were reported, of which 1 patient <1 year old and 1 patient aged 16 (Figure 7.6.3). The 16-year-old patient was vaccinated with NeisVac-C when 16 months old and is therefore considered a vaccine failure. The patient did not have underlying disease. This is the fifth case of vaccine failure since the introduction of the conjugated MenC vaccine in 2002. Of the four remaining vaccine failures, two had an immune deficiency. Up to August 2018, three MenC cases in 45-64 years old were reported (Figure 7.6.3). None of the MenC cases in 2017 and 2018 died.

7.6.3.3 Meningococcal serogroup W

The incidence of MenW disease has been increasing since 2015, with an incidence of 0.29 per 100,000 in 2016 and 0.47 per 100,000 in 2017 (Figure 7.6.1). In 2017, 40% of all meningococcal cases were serogroup W. A total of 80 cases of MenW disease were reported in 2017, with 78 reported up to August 2018 (Figure 7.6.2). In 2018, MenW accounted for 51% of all meningococcal disease cases, and more MenW than MenB cases were reported.
MenW disease occurs across all ages, however peaks in incidence are seen in <5 year olds, especially <2 year olds, and 14-24 year olds (Figure 7.6.4). Furthermore, the incidence increases with age starting from 45-50, with high incidence in 65+ year olds. Since 2015, 17% (35/212) of the cases have died. Deaths occurred in nearly all age groups, with the highest case fatality rate in 14-24 age group (13/45=29%).
Because of the continuing increase of MenW disease, since May 2018 the MenC vaccination given at 14 months has been replaced by a quadrivalent MenACWY vaccination. From October 2018, children aged 13-14 will be offered MenACWY vaccination. In 2019, there will be a catch-up campaign for all children aged 15-18.

7.6.3.4 Meningococcal serogroup B

The incidence of meningococcal serogroup B (MenB) disease has been steadily declining since the late nineties, and has stabilised at an incidence of 0.5 per 100,000 since 2011 (Figure 7.6.1). In 2017, 41% of all meningococcal cases were serogroup B. In total, 81 cases of MenB disease were reported (Figure 7.6.2), showing a slight increase since 2014. In 2018, up to August, 56 MenB cases were reported, similar to the same period in 2017 (n=55). The incidence of MenB disease was still highest in children aged under 5 in 2017 (3.2 per 100,000, n=28) and 2018

(4.3 per 100,000, n=25 up to August), followed by 15-24 year olds with an incidence of 1.1 per 100,000 (n=24) in 2017 and 0.6 per 100,000 (n=9) up to August 2018 (Figure 7.6.5).
The case fatality rate was 6.3% (5/79) in 2017 and 4.9% (77/1561) from 2004-August 2018.

7.6.3.5 Meningococcal serogroup Y

The incidence of meningococcal serogroup Y (MenY) disease was lower than 0.10 per 100,000 up to 2016, and increased slightly in 2017 to 0.16 per 100,000 (Figure 7.6.1). In 2017, 14% of all meningococcal cases were serogroup Y and 27 MenY cases were reported (Figure 7.6.2). Up to August 2018, 15 MenY cases have been reported. Most cases were aged 65 or older (19/27 in 2017 and 6/15 in 2018). No deaths were reported in 2017, and one death was reported in 2018.

7.6.3.6 Other meningococcal serogroups

In 2017, one case of meningococcal serogroup E disease was reported (Figure 7.6.2). In 2018 up to August, 1 case of meningococcal disease due to a non-groupable meningococcus was reported.

7.6.4 Pathogen

In 2017 and 2018, three adult MenC cases were reported (2 males, 1 female) with finetype P1.5-1,10-8:F3-6, the finetype that recently caused an outbreak in Tuscany, Italy [3]. This finetype is also associated with several outbreaks among MSM in past years in various countries [4].

Almost all serogroup W strains from 2015 to 2017 had the same finetype P1.5,2:F1–1 (122/134; 91%) and belonged to clonal complex 11 (cc11; 117/124; 94%) [5]. The incidence of serogroup W IMD not belonging to cc11 has remained stable in recent years with 1-5 cases per year, whereas the number of serogroup W cc11 cases started to increase in 2015. Cluster analysis of all available genome sequences of serogroup W cc11 meningococci isolated in 2012-2017 from Dutch patients shows that isolates from the same year seem to cluster, i.e. the genetic distance between isolates is smaller within years than between years (Figure 7.6.6). Furthermore, within the same year several separate clusters can be discerned, which may suggest different introductions or, more likely, expansions of subclones. These genetic clusters were neither epidemiologically nor geographically associated.

Since 2016, a (regional) increase was observed in the number of MenB cases with finetype P1.22,14:F5-1, which caused three MenB cases in 2016, twelve cases in 2017, and four up to August 2018. Previously, this finetype was only detected in one MenB case in 2009 and two cases in 2014. Of the 19 cases since 2016, 14 lived in the south-west of the Netherlands, of which ten in the region of Rotterdam. Most cases (10/19) were 15-24 years of age.

7.6.5 Research

A study was conducted to evaluate whether MenW cases differed from MenB cases regarding the clinical picture and the severity of the disease. Data were analysed for the years 2015-2017, covering the time period from the increase of MenW cases in the Netherlands. On average, MenW cases were older than MenB cases (median age: 53 vs 18 years, p<0.001). Among MenW

cases, 65.2% were female, compared to 55.0% among MenB cases (p=0.06). MenW cases more often presented with septicaemia/septic shock without meningitis (57/133, 42.9%) compared to MenB cases (49/210, 23.3%; p<0.001), while MenB cases more often presented with only meningitis (116/210, 55.2%) compared to MenW cases (22/133, 16.5%; p<0.001). Additionally, MenW cases more often presented with pneumonia (17/133, 12.8%) or arthritis (5/133, 3.8%) compared to MenB cases (pneumonia: 3/210, 1.4%; p<0.001; arthritis: 1/210; p<0.05). Since 2017, questions about symptoms at disease onset were added to the surveillance questionnaire. Among MenW cases, 19.0% (15/79) reported having had diarrhoea, whereas diarrhoea was reported in only 3.8% (3/78) of MenB cases (p<0.01). Among those with diarrhoea, MenW cases had (11/79, 13.9%) diarrhoea more often without specific symptoms for meningococcal disease like petechiae or neck stiffness compared to 2.6% (2/78) among MenB cases (p<0.01). The case fatality rate of MenW was 12% (17/133), significantly higher than for MenB (4%, 8/211, p=0.004). MenW cases continued to have a more severe outcome of the disease even after adjusting for age and clinical manifestations (OR: 2.9, 95% CI: 1.0-8.6; p<0.05). MenW cases were more severe and associated with different clinical manifestations and presentation compared to MenB cases, independent of the differences in age distribution.

For surveillance of meningococcal disease in the Netherlands, laboratory data from the Netherlands Reference Laboratory for Bacterial Meningitis are linked with notification data from the regional Public Health Services. The surveillance system was evaluated for data completeness and timeliness. A total of 2,123 cases were reported in the years 2004-2016, of which 1,840 (87%) were reported by both data sources. The serogroup was known in 86% of all cases, and this was significantly higher (93%) in the years 2012-2016. Information on vaccination status, mortality and country of infection was available in 88%, 99% and 97% of all *notified* cases, respectively. Regional notification of cases occurred within one working day for 86% of cases and 98% were notified nationally within three working days. This demonstrates a well performing surveillance system. Reporting to both the Netherlands Reference Laboratory for Bacterial Meningitis and the regional Public Health Service remains important to further improve the overall performance in supporting public health response and vaccination policy.

The vaccine response after a primary quadrivalent MenACWY vaccination (Nimenrix) in an older adult cohort (50 - 65) was determined in the Stimulage study resulting in protective antibody titers against the serogroups MenCWY in the vast majority of the participants, lasting for at least one year [6]. These study results were compared with the vaccine responses induced by the quadrivalent MenACWY vaccine in adolescents in the JIM study [7, 8], at least for MenW and MenY because it is a primary vaccination for these 2 serogroups for both age cohorts, while it is obviously a booster vaccination for serogroup MenC in the adolescent age groups [9]. Lower post-vaccination functional antibody titers against MenW and MenY were observed in the older adults compared to the adolescents, resulting in a significantly higher proportion of older adults one year post-vaccination with an rSBA titer below the protection level. A large reduction in post-vaccination IgM concentrations was observed in the middle-aged adults, whereas IgG concentrations were only marginally different between the two age groups. Although protective antibody titers were initiated after primary meningococcal

vaccination in the older adults, antibody functionality was significantly lower compared to that in adolescents, which was mainly caused by lower IgM responses.

In a small dose-finding study, different fractional doses of two quadrivalent meningococcal ACWY vaccines (Menveo and Nimenrix) were administered intradermally to sequential groups of four participants, according to an adaptive dose escalation design starting at 1/10th of the original dose[10]. Booster doses were given after 4–6 months. A 1/10th dose of Menveo resulted in less than complete seroprotection for serogroup A but complete protection against the other serogroups. A 1/10th and 1/5th dose of Nimenrix resulted in complete seroprotection against all four vaccine serogroups. No serious adverse events were found, only mild of nature. These results show that fractional intradermal vaccination with MenACWY appeared to be safe and effective; this should be confirmed in a larger non-inferiority study.

A cost-effectiveness analysis of using MenACWY vaccine was performed to support policy makers in their numerous decisions around the adequate response to the rising number of MenW cases. In this analysis the direct and indirect effects of vaccinating different age-groups with MenACWY were quantified. This was done by projecting MenW disease until 2028 based on the outbreak up to February 2018, in combination with a projected impact of vaccination on disease and carriage of MenW. The analysis revealed that vaccinating young children and adolescents (with or without including a catch-up programme targeting those aged 15 -18) will reduce the number of cases among those vaccinated substantially with a similar cost-effectiveness ratio (~31.000/QALY for 14-month old children, ~28.000 for 14-month old children and 14-year old children, and ~25.000 for 14-month old children and 14-18-year old children). However, there is uncertainty on whether the transmission of MenW can be controlled completely by a vaccination programme because the exact degree of effectiveness of MenACWY vaccination against carriage of MenW is unknown, and, although the age distribution of clinical cases suggests a dominant role of adolescents in MenW transmission, other (older) age groups probably also contribute to the transmission. This combined makes complete control of transmission of MenW less likely.

7.6.6 International developments

7.6.6.1 MenW disease

France reported a cluster of two MenW cases at a university in Paris. The two cases occurred in February and May 2017 and the isolates of these patients were closely related (both were W:P1.5,2:F1-1:cc11) [11]. A vaccination campaign was organised among students staying in Paris during the summer holidays, as well as those who were going to follow a summer course in June. A total of 186 students were vaccinated in June 2017. After the vaccination campaign, no more cases occurred among the student population at this university [personal communication C. Bassi, June 2018].
Hong et al. described the recent epidemiological trends of MenW disease in France and explored the microbiological and epidemiological characteristics associated with different MenW:cc11 sub-lineages for 148 cases in the period 2010-2016 [12]. An increase in MenW disease was observed in 2012 and was linked to isolates belonging to the “Anglo-French-Hajj” sub-lineage. These isolates have decreased significantly since 2013 and have been replaced by

MenW:cc11 isolates related to the "South American-UK" sub-lineage which caused a marked increase in the number of MenW cases in 2016. In this sub-lineage, the "original UK strain" was first detected in 2012 and increased thereafter, followed by the recently described "UK 2013-strain". The case fatality rate of MenW cases in 2015-2016 was significantly higher than for MenBCY cases (22% vs 10%). Among cases due to the "UK 2013-strain", 94% were aged 15 and over, and the case fatality rate was 28%.

A French study explored a large cohort of patients with invasive meningococcal disease (IMD) initially presenting with abdominal symptoms for association with particular meningococcal strains [13]. A total of 105 IMD cases were identified between 1991 and 2016, who presented with a least one of the following criteria (1) abdominal pain, (2) gastroenteritis with diarrhea and vomiting, or (3) diarrhea only. A sharp increase in the number of patients with abdominal symptoms has been observed since 2014. A higher case fatality rate of 24% was observed in cases with initial abdominal presentation compared to 10% in all IMD in France (p=0.007). Isolates of group W were significantly more predominant in these cases compared to all IMD. Most of these isolates belonged to clonal complex 11 of the sublineages of the "South American-UK" strain.

7.6.6.2 MenACWY vaccination

In the US in 2005, meningococcal conjugate vaccine (MenACWY) was recommended for routine use among adolescents aged 11–18. By 2015, vaccine coverage with at least one dose of MenACWY among adolescents aged 13–17 had reached 81.3%. MacNeil et al. describe the epidemiologic features of meningococcal disease and trends in meningococcal disease incidence following MenACWY introduction in the United States in the period 2006-2015 [14]. The annual incidence of meningococcal disease was 0.26 cases per 100,000 population (7,924 cases); 15% of cases were fatal. The serogroup distribution was: 36% serogroup B, 29% serogroup Y, 23% serogroup C, 7% serogroup W, and 6% other serogroups. The incidence of serogroups A, C, W, and Y combined declined 76% among people aged 11–20 from 2006–2010 to 2011–2015 (p<0.0001). From 1996 through 2015, the incidence of meningococcal disease declined among all age groups and predominant serogroups. Reductions in the incidence of meningococcal disease due to serogroups A, C, W, and Y among adolescents suggest an impact of the MenACWY vaccine programme in this age group.

7.6.6.3 MenB vaccination

In 2017, recombinant protein MenB vaccine (MenB-FHbp [bivalent rLP2086; Trumenba®]) was approved for protection against MenB infection in persons ≥10 years of age in the European Union as a 2 or 3-dose primary vaccination schedule. Beeslaar et al. reviewed the current evidence on administration of MenB-FHbp as a 2-dose primary vaccination schedule [15]. The authors conclude that findings to date suggest that the 2-dose MenB-FHbp regimen administered at 0 and 6 months is appropriate for routine vaccination programmes.
In contrast, a 3-dose schedule administered at 0, 1–2, and 6 months is more suitable when targeting individuals at high risk of IMD or for outbreak control.

7.6.7 Literature

7.6.7.1 References

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7.7 Mumps

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7.7.1 Key points

- The incidence of mumps in 2017 was low (0.3 per 100,000), and slightly lower than in the previous two years.
- Most of the mumps cases in the Netherlands were caused by mumps virus genotype G.

7.7.2 Tables and figures

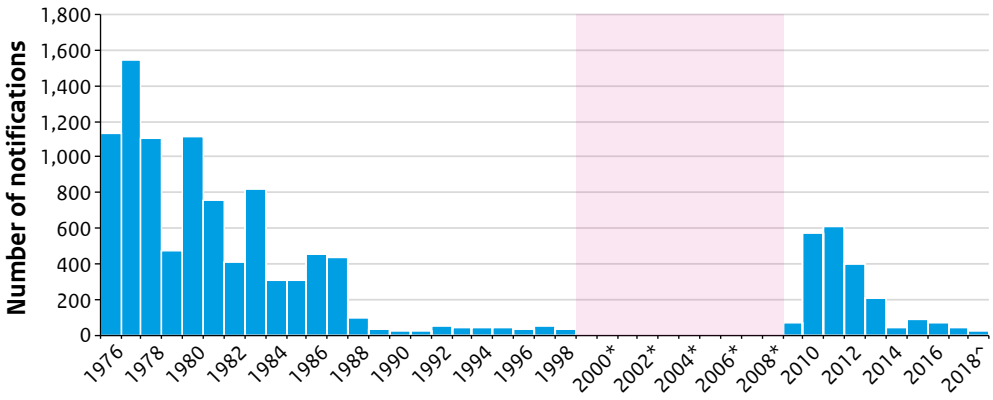

Figure 7.7.1 Number of notified mumps cases in the period 1976-2017
* In the period 1999-2008 mumps was not notifiable
^ Up to July
Source: Osiris

7.7.3 Epidemiology

Following the introduction of mumps vaccination in the NIP in 1987, there was a large decline in the incidence of mumps in the Netherlands. First signs of an increase were observed in 2004 with an outbreak of 105 cases among (mainly vaccinated) students [1]. Subsequently, an outbreak occurred in 2007-2009 (i.e. notifications by law only started again in 2008) among unvaccinated schoolchildren in the so-called 'Bible Belt'. In this period, 275 cases were reported in a sentinel general practitioner database [2]. From late 2009 until 2012, a countrywide epidemic with over 1500 reported cases occurred that once more especially affected (vaccinated) student populations (Figure 7.7.1) [3]. Since 2012, the number of reported mumps cases among students has declined in the Netherlands.

In 2017, the incidence of mumps was low with 46 reported cases (Figure 7.7.1). More males than females patients were reported (71.7%), the mean age was 26 (range 0-57). Twenty were twice vaccinated, seven once vaccinated, one vaccinated with an unknown number of doses, 15 were unvaccinated and the vaccination status was unknown for three. One of the unvaccinated cases was an 11-month-old child who was too young to be vaccinated. Only 11 cases were students. One third of the cases were imported or likely to be imported. Two patients were hospitalised; an unvaccinated child with a parotid abscess and an adult with orchitis. Another five patients (three of them twice and one once vaccinated) reported orchitis and one unvaccinated patient had an ear infection.

Three small clusters were identified in 2017; two household clusters of two patients who infected their partners, of which one index was infected abroad. Another cluster consisted of four students aged 13 - 17 who were linked through school and a hockey club. The most likely index case was an exchange student from South Africa who had mumps-compatible symptoms, but was not tested.

In 2018, until 30 June, 25 mumps cases have been reported. About half of the cases were male (n=12) with mean age 30.9 (range 3-66), four were students, and 3 acquired the infection abroad. Most were sporadic mumps cases, except for two clusters. The first cluster was reported in February from an asylum seeker centre and consisted of six patients from Cuba of whom five were twice vaccinated. The other cluster consisted of family relatives and included three patients.

7.7.4 Pathogen

Since 2010, most of the mumps cases in the Netherlands have been caused by mumps virus genotype G. In 2017 and the first six months of 2018, a genotype was obtained from mumps viruses detected in 29 cases. The majority (68%) of these cases was genotype G. In addition, some other mumps virus genotypes were detected in a relatively low number of cases in 2017/2018; genotype H (4 cases; 14%), C (2 cases; 7%), D, J and K (each one case; 4%). Many of the infections with mumps viruses of the non-G genotypes could be related to import or travel to countries where these mumps virus genotypes are currently circulating, such as India and Vietnam [4].

7.7.5 Research

RIVM performs multi-disciplinary research to gain insights into the cause of the occurrence of mumps outbreaks among young vaccinated adults and to create possible solutions.

7.7.5.1 *Cellular immunity*

The decline in vaccination-induced antibodies is thought to increase the risk of vaccine failure over time. However, based on data from our recent study, we hypothise that the induction after vaccination of a suboptimal T-cell response may also play a role [5]. In this study, it was shown that after mumps infection, mumps-specific IFN-γ responses were dominated by CD8+ T cells, but not after vaccination. Moreover, the mumps-specific CD8+ T cells in mumps cases showed a persistent polyfunctionality (i.e. secretion of various cytokines, cytotoxic features), while the CD8+ T cells observed in recently vaccinated children lacked polyfunctionality.

7.7.5.2 *Clinical MMR-3 study*

A third dose of MMR could be an effective intervention to control outbreaks among vaccinated persons, but evidence regarding immunogenicity, safety and effectiveness is limited. To date, only one study is available decribing two different clinical cohorts and immunogenicity data following a third MMR vaccination [6]. To gain more insights, a clinical study was initiated in October 2016 to study the safety and the short and long-term mumps-specific humoral and cellular immunity of a third dose of MMR vaccine in young adults. In agreement with the study by Fiebelkorn et al.[6], our MMR-3 study indicates that giving a third dose of the MMR vaccine to young adults is safe. No serious adverse events were reported. A significant increase in mumps-specific IgG concentrations and virus neutralising antibodies against mumps virus were observed 1 month after vaccination. Immunogenicity data 1 year after MMR-3 vaccination are expected in 2019.

7.7.6 International developments

In response to the increased number of mumps outbreaks reported in the United States since late 2015, the Advisory Committee on Immunisation Practices (ACIP), i.e. public health experts that develop recommendations on use of vaccines in the United States, recently recommended the use of a third dose of MMR(V) vaccine (with or without varicella component) in persons at increased risk for mumps during an outbreak [7]. This recommendation was based on results from three epidemiological studies that provided evidence that persons that had received a third dose of MMR had lower attack rates in an outbreak setting [8-10]. Cardemil et al. described an outbreak in the US in 2015/2016 in which 259 students got mumps. The attack rate in 5,000 students who received a third MMR vaccine dose was lower than in the 15,000 twice MMR vaccinated students (6.7 vs 14.5 cases per 1,000). Students who received the second MMR vaccine dose more than 13 years ago, had a 9 - 14 times higher risk of getting mumps than those who received the second MMR vaccine dose more recently. In the US, the second MMR vaccination is given at the age of 4-6 years.

7.7.7 Literature

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* RIVM publication

7.8 Pertussis

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7.8.1 Key points

- In 2017, there were no major changes in the pertussis epidemiology; the incidence rate was 28.7 per 100,000 compared with 32.6 per 100,000 in 2016.
- In 2017, only three prn-deficient isolates (9.7%) were found compared to 12% in 2016.
- Maternal pertussis vaccination will be implemented in the NIP in 2019.

7.8.2 Tables and figures

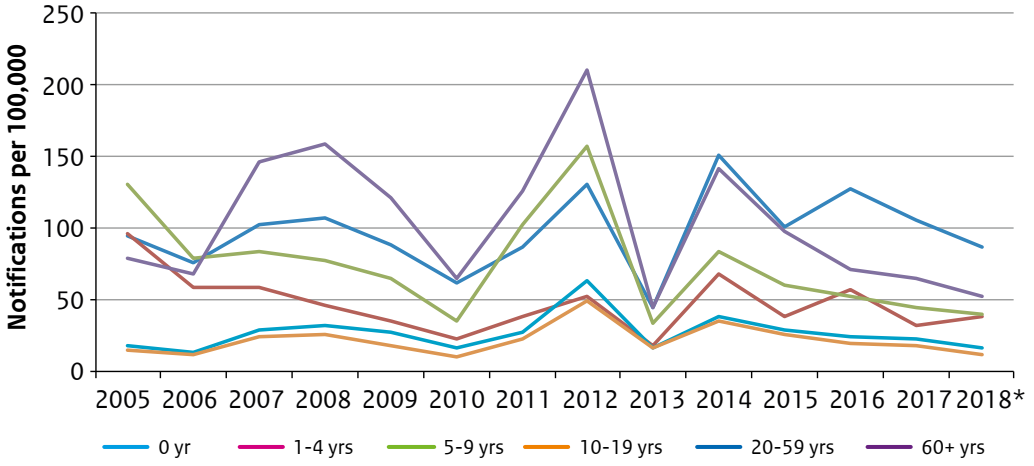

Figure 7.8.1 Pertussis notifications per 100,000 per age category for 2005-2018*
*reports up to April 1st, 2018 are included

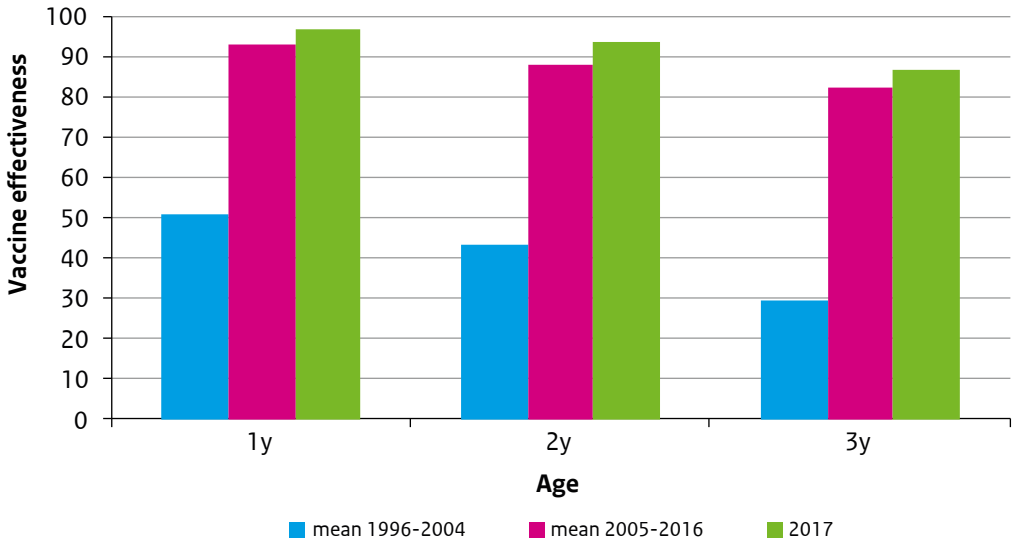

Figure 7.8.2 Vaccine effectiveness, calculated with the screeing method (96% population coverage), estimated for 1, 2 and 3-year-olds during use of whole cell pertussis vaccination (mean 1996-2004) and during use of acellular pertussis vaccination (mean 2005-2016 and 2017 separate)

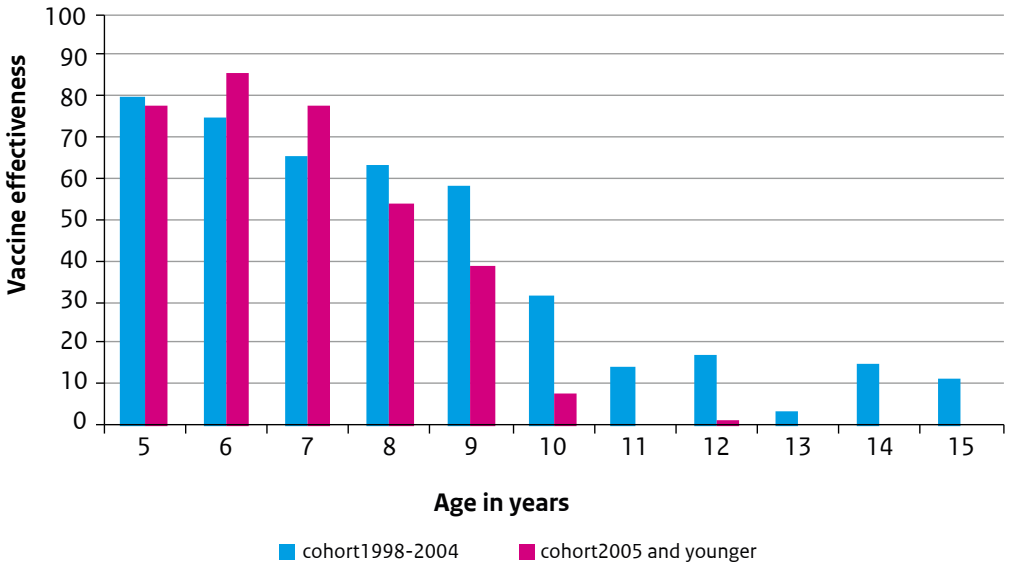

Figure 7.8.3 Mean vaccine effectiveness, calculated using the screening method (92% population coverage), estimated for 5 - 15-year-olds for cohorts with whole cell pertussis priming (cohort1998-2004) and acellular pertussis priming (cohorts 2005 and younger). Not all cohorts of 2005 and younger have yet reached the age of 10-15 years.

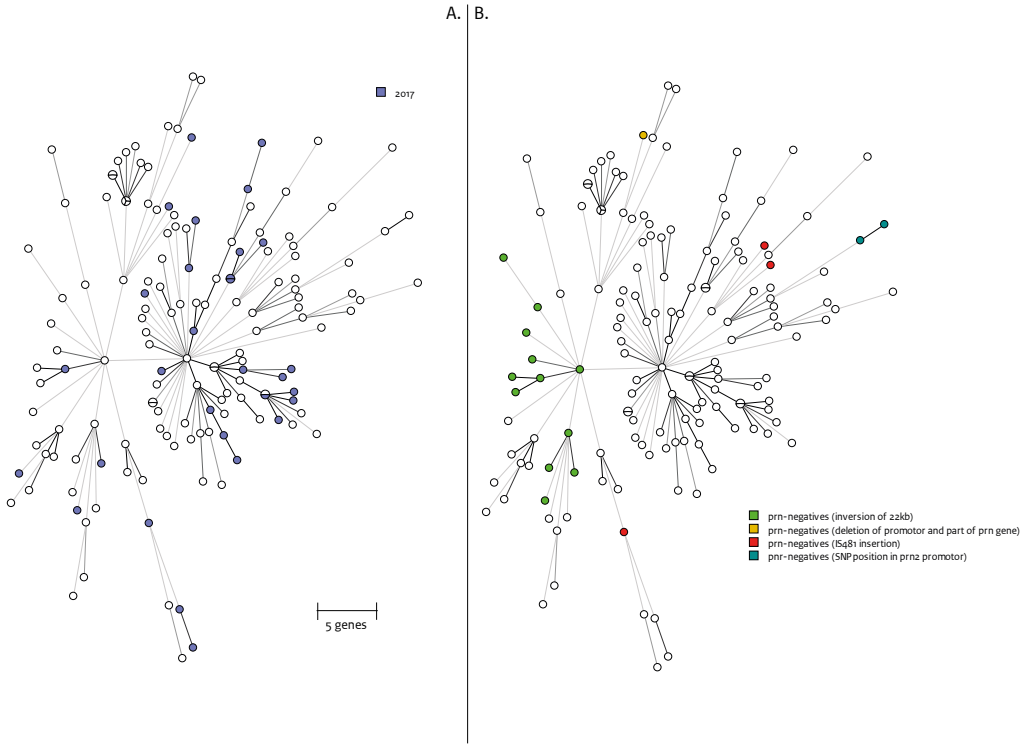

Figure 7.8.4 Minimum spanning tree of *B. pertussis* isolates from 2015 to 2017 (n=150).
Each node in this spanning tree based on 3,180 genes in the cgMLST scheme represents a single *B. pertussis* isolate from the Netherlands. The length of the lines between isolates represent the number of different genes. In the left panel (A), the isolates coloured in blue represent the isolates submitted in 2017. The right panel (B) shows the distribution of the prn-deficient isolates over the years 2015, 2016 and 2017.

7.8.3 Epidemiology

7.8.3.1 Disease

In 2017, the overall incidence rate (IR) of pertussis notifications was somewhat lower than in 2016 (28.7 per 100,000 vs 32.6 per 100,000). For all age categories, IRs of 2017 were also lower than in 2016 (Figure 7.8.1). Looking at the 1st quarter 2018 data, again we note lower IRs. As the last increase in pertussis notifications was observed in 2014, a new peak is expected in the near future (based on the usual 3-4y peak pattern).
Hospitalisation data for 2015-2017 are not yet available.
Statistics Netherlands reported two pertussis related deaths in 2017, one 0-year-old boy and one woman aged between 85-90. One male between 75 and 80 years with unknown vaccination status was reported to have died due to pertussis.

7.8.3.2 *Vaccine effectiveness (VE)*

Figure 7.8.2, shows VE estimated through the 'screening method', for the infant vaccination series. We would like to emphasise that the presented VE should not be interpreted as 'true' absolute estimates of effectiveness, but for studying trends in VE estimations. In 2005, an infant combination vaccine with an acellular pertussis component replaced the whole-cell pertussis vaccine containing combination vaccine, resulting in an increase of VE of the primary series for 1-3 year-olds. Since then, VE of the primary series has been continuously high.
VE of the booster dose at 4 years of age decreases when children reach the age of 8 i.e. 4-5 years after the booster vaccination, especially in epidemic years (Figure 7.8.3).

7.8.4 Pathogen

The strain surveillance focusses on the genotypic and phenotypic changes of the *Bordetella pertussis* population in the Netherlands. For this, confirmed *B. pertussis* strains are subjected to whole genome sequencing and an antigen expression method for the pertussis antigens; pertussis toxin (Ptx), pertactin (Prn) and filamentous hemagglutinin (FHA). In 2017, a total of 112 *Bordetella* suspected cultures were received from 12 different medical microbiology laboratories, a decline in submission of 28% compared to 2016. A *B. pertussis* was retrieved in 31 of the 112 suspected cultures (28%). Besides *B. pertussis,* two *B. Holmesii* strains were found.
Whole genome sequencing of all *B. pertussis* isolates showed that all isolates had alleles ptxP3, prn2 and ptxA1, while most isolates belonged to MLVA-type (MT)27 (*n* = 20) a type that was also predominant in previous years (2015-2016). A phylogenetic tree, based on 3,180 genes in the core-genome multiple-locus sequence typing (cg-MLST) scheme shows that the 2017 isolates were scattered over the tree, indicating that multiple *B. pertussis* strains are circulating in the Netherlands (Figure 1, panel A).
We have seen the emergence of *B. pertussis* isolates deficient in vaccine component prn in the Netherlands between 2010-2015, reaching a 15% prevalence in 2015. There was a minor decline in 2016 to 12%, and in 2017, the number and prevalence of prn-deficient isolates further declined. In 2017, only three prn-deficient isolates (9.7%) were found compared to 12% in 2016. The prn-deficiency of the three isolates in 2017 was caused by either a large inversion of 22kb (*n*=2) or an insertion of the IS481 element in the promotor region of prn (*n*=1). In 2016, the composition of the prn-deficient isolates was also fully comprised by either the 22kb inversion (*n*=5) or the insertion of IS481 (*n*=1). Plotting the prn-deficient isolates from 2015-2017 on the phylogenetic tree shows that the isolates that have the large inversion seem to cluster whereas the other causes were more scattered (Figure 1, panel B). In addition to prn-deficiency, two isolates originating from 2015 and 2016 were shown to be FHA-deficient. However, in 2017 no further FHA-deficient isolates were found.
Another recently observed shift was the increase of the fim3-2 strains. In 2010, this genotype was first seen, but more than 65% of the *B. pertussis* isolates had this genotype in 2016. In 2017, 20 of the 31 (65%) *B. pertussis* isolates were fim3-2, showing a stagnation in the rise of this phenotype.

7.8.5 Research

7.8.5.1 Cost effectiveness

Using US data, cost-effectiveness of a practice based intervention to improve the uptake of influenza and diphtheria, tetanus and acellular pertussis (DTaP) vaccination in adults aged under 65 was evaluated [1]. The so-called 4 Pillars Practice Transformation Programme is an intervention in primary care including convenient vaccination services, communication with patients about the importance of immunisation and the availability of vaccines, enhanced office systems to facilitate immunisation, and motivation through an office immunisation campaigner who monitors progress and encourages adherence to vaccination-promoting office procedures. From a societal perspective, taking productivity losses into account, the incremental cost-effectiveness ratio was $31,700 per QALY gained. The model results were largely driven by influenza-related parameters. In another economic evaluation, the intervention was studied with respect to influenza, pneumococcal disease, and DTaP for adults aged under 65 with high risk of illness complications [2]. Here, the intervention was cost-saving, mainly due to a reduction of influenza cases by 1.4%.

From March 2015, maternal DTaP vaccination in the third trimester of pregnancy is recommended in Australia, but this is not funded nationally. In an economic evaluation, the cost-effectiveness was assessed for adding maternal DTaP vaccination to the 2016 nationally-funded pertussis program (DTaP at 2, 4, 6, 18 months, 4 years and at 12-13 years)[3]. In the study, vaccine effectiveness against pertussis infection was assumed to be 92% in mothers with duration of protection of 5 years, and 91% in newborns. From a healthcare perspective, the ICER of adding maternal vaccination was AU$ 32,065 per QALY gained.

7.8.5.2 Immunology

Longitudinal data on anti-PT IgG concentrations showed high antibody concentrations for three consecutive years in 41% of the participants with a cut-off ≥50 IU/ml. Therefore, a PT-IgG concentration ≥50 IU/ml as indication for recent pertussis infection may lead to an overestimation of these numbers in cross-sectional serosurveillance studies, and should therefore be used carefully [5]. After the pre-school booster vaccination, IgG levels were significantly higher in aP-primed compared with wP-primed children aged up to 6. Importantly, the Tdap booster vaccination induced less vaccine antigen-specific IgG, B-cell and Th1 responses, resulting in a significantly lower Th1/Th2 ratio in aP-primed compared with wP-primed children. These results indicate that replacement of the Dutch DTwP-combination vaccine by DTaP-combination vaccines results in a less favourable immune response with a decreased Th1 profile in the currently DTaP-primed children versus DTwP- primed children [6-7]. This is in line with international epidemiological data showing that DTaP-primed adolescents are less protected against clinical pertussis than wP-primed children.
A first booster vaccination in adults aged 25-29 primed with wP vaccines induced robust humoral and cellular immunogenicity that remained higher for up to 2 years compared with pre-booster levels, and will most likely confer protection against pertussis in these adults. Furthermore, antibody levels are predicted to remain above the presumed protective cut-off value (20 IU/ml) for at least 9 years; this deserves further attention when evaluating the current recommendation to revaccinate women during every new pregnancy [8].

Several clinical and experimental immunological studies further underpinned our understanding of the emergence of new *B. pertussis* strains and of the suboptimal duration or effectiveness of immune responses after current vaccination compared to natural infection. Recent findings indicate that emerging *B. pertussis* strains, particularly those circulating after the introduction of the aP vaccine, induce stronger activation of specific innate immune receptors and higher levels of the anti-inflammatory cytokine IL-10 by dendritic cells [9]. Ongoing studies address mechanisms of innate immune cells which are crucial in limiting *B. pertussis* infection, and the role of various *B. pertussis* antigens in evading these mechanisms. Collective findings in recent years further highlight the virulence and immunomodulatory capacity of this pathogen, results of which were published and described in a doctoral thesis [10-12]. Studying a large cohort of (ex-) pertussis cases revealed the significant impact of type of primary vaccination and age on the immune responsiveness and memory to *B. pertussis* [13, 14]. Internationally, the scientific community is calling for the development of a next generation pertussis vaccine with an improved immunological signature. In experimental models using a systems biology approach, collaborative studies of RIVM with IntraVacc in recent years have advanced our basic knowledge on the differences between immunity after priming with classic wP vaccine, current aP vaccine, and several candidate vaccine concepts [15-19].

7.8.6 International developments

Within the framework of the EUPertstrain group, a collaboration between the European experts on whooping cough, a project for (improvement of) the serosurveillance of pertussis is being funded by the ECDC. RIVM is leading the organisation of a seroprevalence study in European countries for pertussis and diphtheria in the age groups 40-60. At the moment, sufficient samples (500 per country) have been received from 14 countries, and possibly 4 others will also participate. The measurements of the antibody levels with the DTaP-MIA are ongoing.

The Periscope consortium consisting of pertussis experts from 16 European universities, 4 national institutes including the RIVM, and 2 vaccine companies received support for their extensive IMI-2 proposal with the main objective of unravelling the reduced protective properties of the aP vaccines compared to wP vaccines and natural infection touching a large range of (immunological) disciplines, and to characterise new biomarkers for pertussis immunity. In addition to human vaccine trials, studies in the mouse model and baboon model, human challenge studies, and naturally infected studies, are part of this €28 million proposal. The main role of the RIVM is to conduct clinical vaccine studies and a natural infection study (Immfact) and perform and/or develop immunological assays for the measurement of antibodies, B-cells and T-cells. Recruitment for the booster vaccine study (BERT study) involving 4 different age groups who received different existing pertussis vaccines, started in October 2017 and was completed in April 2018. This multi-center study has also started in the UK and Finland. In addition, the effect of priming with a wP vaccine versus an aP vaccine on the development of pertussis immunity will be studied in neonates combined with maternal vaccination (AWARE study). The preparations for this complex multi-centre study are in full progress and the study is expected to start early in 2019.

Furthermore, in autumn 2018, a study will start to improve our understanding of whooping cough resurgence in Europe using a population genomics approach. This project will define the extent and rate of sublineage mixing across Europe, and the interdependence of countries and world regions with regards to the impact of their vaccination strategies, on *B. pertussis* evolution. The project will also define the demographic and adaptive dynamics of *B. pertussis* populations across recent times. For this study, approximately 700 *B. pertussis* isolates from all over Europe will be sequenced.

7.8.7 Literature

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* RIVM publication

7.9 Pneumococcal disease

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7.9.1 Key points

- Introduction of pneumococcal conjugate vaccination (PCV) led to a significant decline in overall invasive pneumococcal disease (IPD) in children aged under 5, 5 - 49 year olds, and in elderly aged 65 years and older.
- The incidence of PCV7 type invasive pneumococcal disease (IPD) remained very low in 2017/2018, with an incidence of 0.7 per 100,000.
- The incidence of PCV10-7 type IPD further declined in 2017/2018 to an incidence of 0.9 per 100,000.
- The increasing trend in incidence of non-PCV10 type IPD continued in 2017/2018.
- The incidence of PCV13-10 type IPD (3.9/100,000), including serotype 19A, was significantly higher than before introduction of PCV7 (118% increase) and PCV10 (59% increase), and higher than the incidence in 2016/2017 (3.2/100,000).
- The incidence of PPV23-PCV13 type IPD in 65+ year olds has increased steadily, from 10.6 per 100,000 in 2004/2005 to 24.4 per 100,000 in 2017/2018.
- Serotype 8, 19A, 3, 22F and 9N were the most common non-vaccine serotypes causing IPD in 2016/17.
- Vaccine effectiveness (VE) of at least two doses of PCV10 was 90% (95%CI 68-97%) against vaccine type IPD.
- A UK study found rapid increases in IPD due to non-PCV13 serotypes, which compromises the benefits of the PCV13 programme in the UK.

7.9.2 Tables and figures

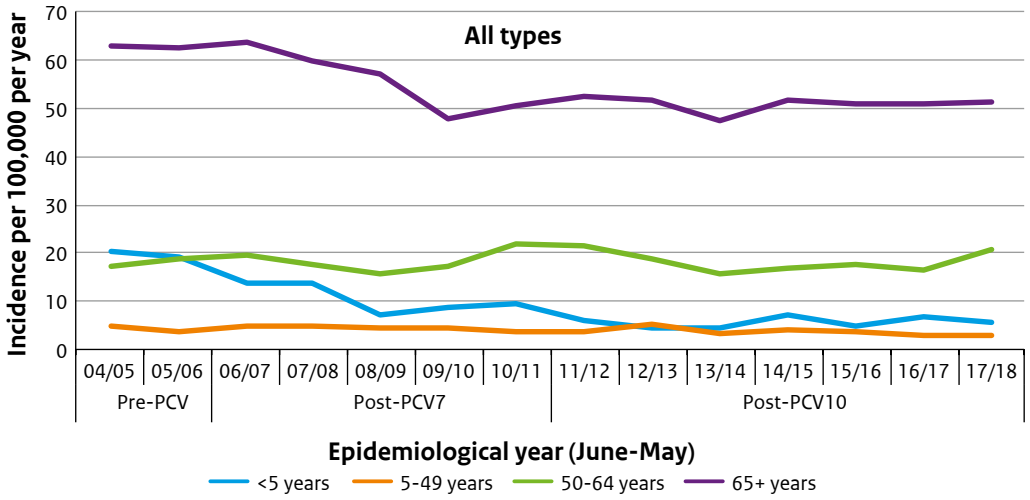


Figure 7.9.1 Incidence of invasive pneumococcal disease (IPD) caused by all serotypes, presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)

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

Source: NRLBM

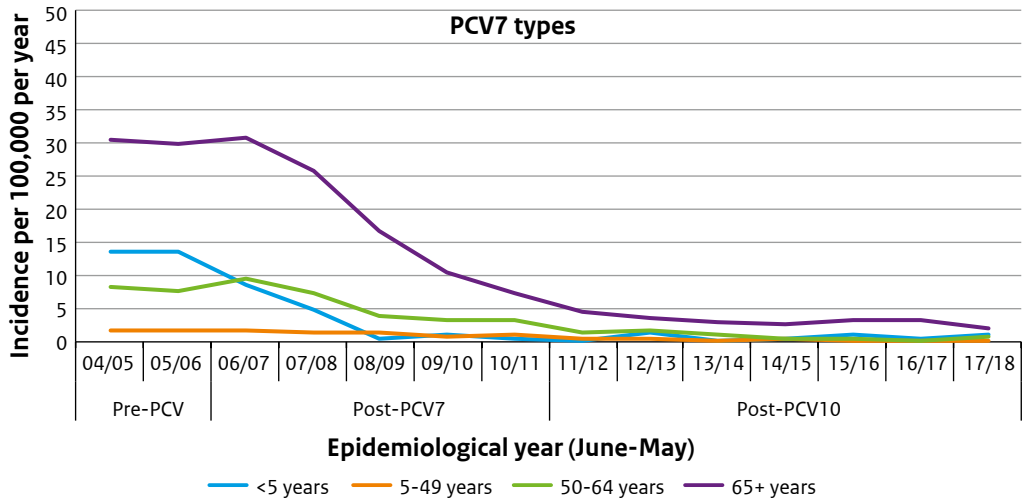
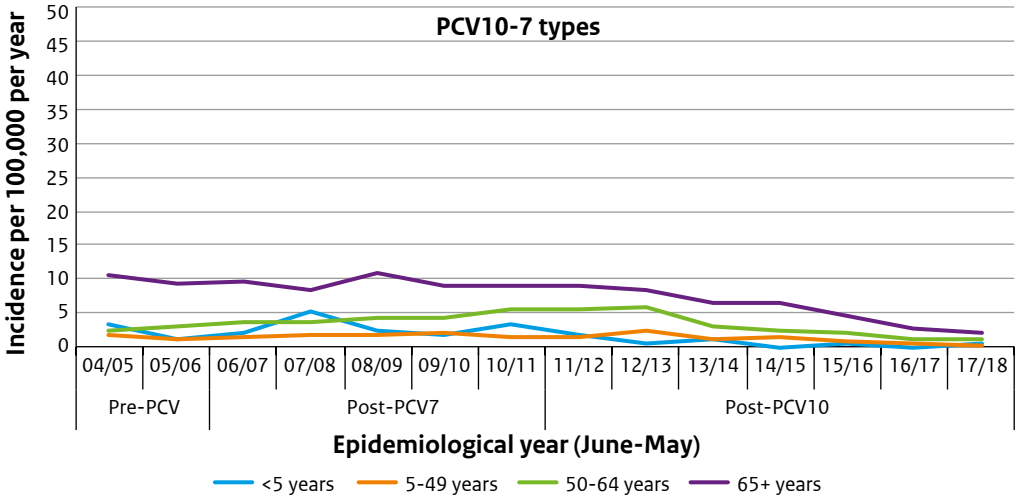


Figure 7.9.2 Incidence of invasive pneumococcal disease (IPD) caused by PCV7 serotypes, PCV10-7 serotypes, PCV13-10 serotypes and non-PCV10 serotypes, presented by epidemiological year (e.g. 04/05 = June 2004-May 2005).

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

Source: NRLBM



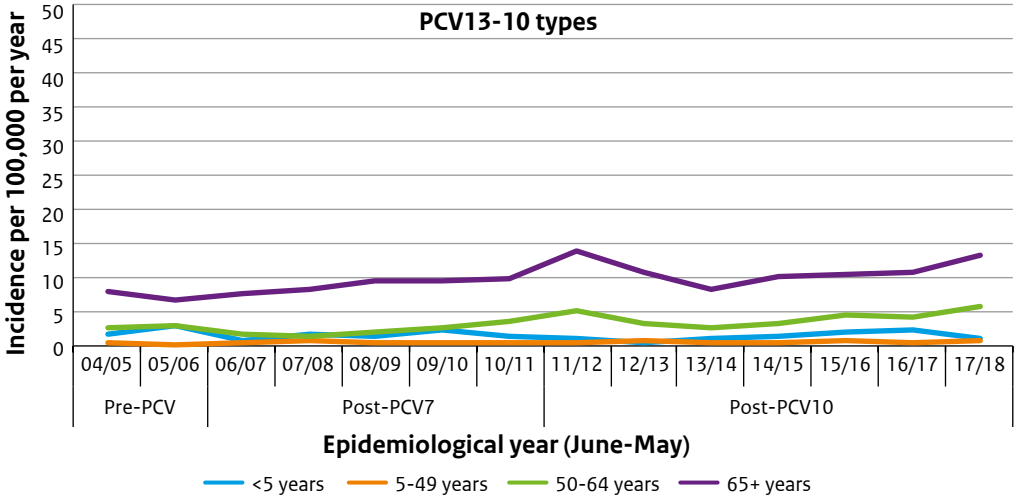


Figure 7.9.2 *(continuation)* Incidence of invasive pneumococcal disease (IPD) caused by PCV7 serotypes, PCV10-7 serotypes, PCV13-10 serotypes and non-PCV10 serotypes, presented by epidemiological year (e.g. 04/05 = June 2004-May 2005).

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

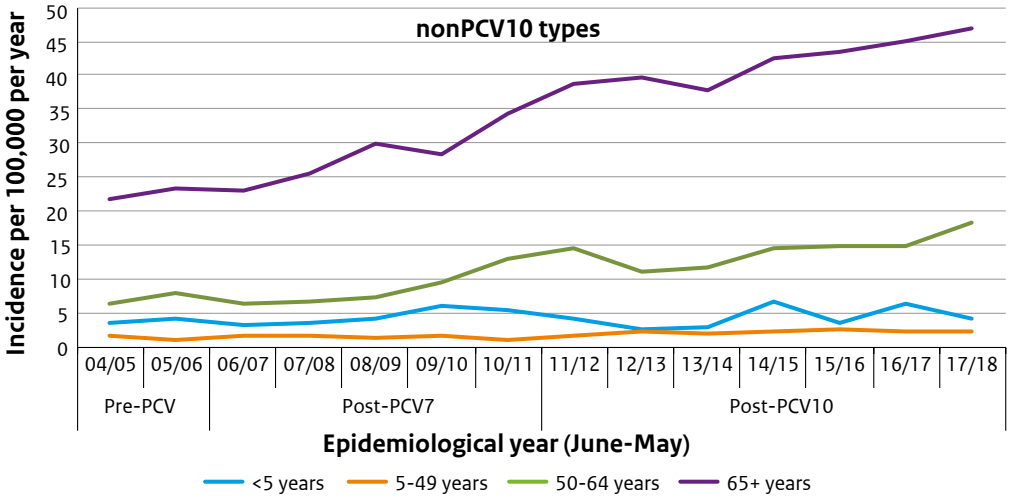


Figure 7.9.2 *(continuation)* Incidence of invasive pneumococcal disease (IPD) caused by PCV7 serotypes, PCV10-7 serotypes, PCV13-10 serotypes and non-PCV10 serotypes, presented by epidemiological year (e.g. 04/05 = June 2004-May 2005).

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

Table 7.9.1 Serotypes included in the different pneumococcal vaccines

Serotype	Vaccine			
	PCV7	PCV10	PCV13	PPV23
4	X	X	X	X
6B	X	X	X	X
9V	X	X	X	X
14	X	X	X	X
18C	X	X	X	X
19F	X	X	X	X
23F	X	X	X	X
1		X	X	X
5		X	X	X
7F		X	X	X
3			X	X
6A			X	
19A			X	X
2				X
8				X
9N				X
10A				X
11A				X
12F				X
15B				X
17F				X
20				X
22F				X
33F				X

Table 7.9.2 Children eligible for vaccination (born since June 2006) with vaccine type invasive pneumococcal disease (IPD) who received at least two vaccinations (with at least two weeks between the second dose and diagnosis) based on nationwide surveillance data using data up to May 2018

Year of diagnosis	Age in months	Serotype	Vaccine received	Number of vaccinations	Underlying disease
2008	3	6B	PCV7	2	?
2008	7	6B	PCV7	3	?
2009	29	19F	PCV7	4	?
2009	6	19F	PCV7	3	None
2010	12	6B	PCV7	4	?
2011	59	19F	PCV7	4	Nephrotic syndrome
2012	63	18C	PCV7	4	None
2012	45	19F	PCV7	4	Leukemia
2012	54	9V	PCV7	4	?
2013	73	19F	PCV7	4	?
2014	68	19F	PCV7	4	CSF leakage, history of meningitis
2014	18	7F	PCV10	4	None
2014	41	23F	PCV10	4	Beta thalassemia with chronic blood transfusi-ons
2015	13	7F	PCV10	3	None
2015	34	19F	PCV10	4	None
2015	50	23F	PCV10	4	?
2016	45	1	PCV10	4	None
2016	25	23F	PCV10	3	None
2017	115	14	PCV7	4	?

Source: NRLBM, Praeventis, Osiris

7.9.3 Epidemiology

7.9.3.1 *Overall invasive pneumococcal disease (IPD) incidence*

In the epidemiological year 2017/2018, 669 IPD cases were reported by the nine sentinel laboratories (covering 25% of the Dutch population). This resulted in an overall IPD incidence of 15.7 per 100,000 in 2017/2018 (Figure 7.9.1). The incidence in 2017/2018 was significantly lower than before the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in <5 year olds (72% reduction), 5-49 year olds (33% reduction) and 65+ year olds (18% reduction). Overall, there was no change in incidence in 2017/2018 compared to 2016/2017

(14.7 per 100,000), although there was a significant 26% increase in 50-64 year olds (from 16.4 to 20.6 per 100,000).

7.9.3.2 *Vaccine type IPD incidence (see Table 7.9.1)*

In 2016/2017, 29 of 669 reported IPD cases (4.3%) were caused by a PCV7 serotype, resulting in an incidence of 0.7 per 100,000 (Figure 7.9.2). The incidence of PCV7 type IPD in 2017/2018 was significantly lower than before the introduction of PCV7 in all age groups (overall reduction of 91%). In 2017/2018, PCV7 type IPD incidence was similar to that in 2016/2017 (0.7 per 100,000) in all age groups.

In 2017/2018, 37 (5.5%) reported IPD cases were caused by the three additional serotypes included in PCV10 (serotype 1, 5 and 7F), resulting in an incidence of 0.9 per 100,000 for PCV10-7 type IPD (Figure 7.9.2). The incidence of PCV10-7 type IPD in 2017/2018 was significantly lower than in the two years before PCV10 introduction in all age groups (overall reduction of 76%). Compared with 2016/2017 (1.1/100,000) there was a further decline in PCV10-7 type IPD incidence in 2017/2018, but this was not significant.

7.9.3.3 *Non-vaccine type IPD incidence*

In 2017/2018, 603 (90%) reported IPD cases were caused by serotypes not included in PCV10, resulting in an incidence of 14.1 per 100,000 (Figure 7.9.2). The incidence of non-PCV10 type IPD in 2017/2018 was significantly higher than before the introduction of PCV7 and PCV10 in all age groups, except for <5 year olds (overall increase compared with pre-PCV7 period was 151%). There were no significant differences between 2017/2018 and 2016/2017 (13.0/100,000) in incidence of non-PCV10 type IPD, although the increasing trend continued.

Of special interest is the group of non-PCV10 type IPD caused by the three additional serotypes included in PCV13, serotype 3, 6A and 19A. In 2017/2018, these serotypes caused 25% (n=168) of the reported IPD cases, resulting in an incidence of 3.9 per 100,000 for PCV13-10 IPD (Figure 7.9.2). This incidence was significantly higher than before the introduction of PCV7 (118% increase) and PCV10 (59% increase), and higher than the incidence in 2016/2017 (3.2/100,000). In children aged <5 and 5-49 year olds, there was no significant difference in incidence of PCV13-10 IPD between 2017/2018 and before the introduction of PCV10.

In 2017/2018, 193 (48%) of the IPD cases among 65+ year olds were caused by serotypes included in the 23-valent pneumococcal polysaccharide vaccine (PPV23) but not in PCV13 (PPV23-PCV13). The incidence of PPV23-PCV13 type IPD in 65+ year olds increased steadily from 10.6 per 100,000 in 2004/2005 to 24.4 per 100,000 in 2017/2018.

Serotype 8, 19A, 3, 22F and 9N were the most common non-vaccine serotypes causing IPD in 2017/2018.

7.9.3.4 *Vaccine failure*

Since the introduction of PCV7, 42 cases of vaccine-type IPD have been reported among vaccine-eligible children (born after April 1, 2006 and aged at least 2 months) in the nationwide surveillance. Of these, 19 children (45%) were vaccinated with at least two doses (with the second dose given at least two weeks before diagnosis), and therefore were considered vaccine failures (Table 7.9.2). Serotype 19F was the most common serotype among vaccine failure cases (n=7, 37%). There was one vaccine failure case in 2017, vaccinated with PCV7.

7.9.3.5 Vaccine effectiveness (VE) against IPD

VE of PCV10 was calculated using the indirect cohort (or Broome) method, in which the odds of vaccination in vaccine type cases is compared with the odds of vaccination in non-vaccine type cases. The population included all reported IPD cases up to December 2017 who were eligible for PCV10 vaccination and aged at least 2 months, and with known serotype and vaccination status.

Seven of the 14 (50%) vaccine type IPD cases were vaccinated with at least two doses, as were 153 of the 168 (91%) non-vaccine type IPD cases. This resulted in a VE of 90% (95%CI 68-97%) for at least two doses of PCV10 compared with zero doses. Serotype-specific VE was 94% (95%CI 58-99%) for serotype 7F. VE against PCV10-related IPD (type 6A, 6C, 6D, 7A, 7B, 7C, 9A, 9L, 9N, 18A, 18B, 18F, 19A, 19B, 19C, 23A, 23B) was 29% (95%CI -110 to 74%) and, specifically, VE against serotype 19A was 53% (95%CI -51 to 85%). From these results, cross-protection of PCV10 against vaccine-related IPD including serotype 19A cannot be confirmed.

7.9.3.6 IPD mortality

From 2014 to May 2018, 233 IPD cases among children aged under 5 were reported nationally. For 155 cases (67%), the mortality status was known. Nine of the 155 (6%) cases died. These nine cases had non-vaccine type IPD (serotypes 3 (n=2), 6C, 8, 12F, 15C, 23A, 22F, 24F) and three had known comorbidity.

7.9.4 Pathogen

No obvious changes in the genetic background of isolates over time were observed.

7.9.5 Research

Pneumococci can undergo a capsular switch, meaning that they exchange capsular genes, thereby changing their serotype. This mechanism may lead to pneumococcal strains that have retained their original virulent traits but express capsules that are not recognised by the vaccine induced immunity. In the period 2004-2016, 135 potential capsular switches were observed based on MLVA typing. These potential capsular switch events took place in 16 different MLVA complexes, but some MLVA complexes seem more prone to capsular switches than others. There was no clear increase in the number of capsular switch events over time, but most suspected events were seen in 2005, 2014 and 2015 with 19, 17 and 21 possible events, respectively. The most frequently observed switches were seen in MLVA complex 9V. Within this MLVA-complex, 19 potential switches were observed between 2004 and 2016, but there appears to be an increase after the introduction of PCV7 and PCV10. To assess whether these potential capsular switches are correctly assigned, whole genome sequencing (WGS) will be applied on a selection of isolates.

Clinical data of ~2400 IPD patients diagnosed between June 2012 and June 2016 were retrospectively collected from medical records, as was previously done for the period June 2004 to June 2012. In the analysis, three periods were defined: pre-PCV period (June 2004-June 2006), PCV7 period (June 2008-June 2011), and PCV10 period (June 2013-June 2016). There was no significant change between the three periods in the proportion of patients presenting with meningitis, bacteraemic pneumonia, bacteraemia with other focus, or bacteraemia without

focus. The incidence of empyema, which increased in the PCV7 period, did not further increase in the PCV10 period. The case fatality rate was 13.4% in the PCV10 period, which was significantly lower than in the pre-PCV period (16.2%), and not significantly different from the PCV7 period (11.8%). There was no difference in the percentage of patients admitted to the ICU between the three periods. The percentage of patients with any comorbidity was higher in the PCV10 period compared with the other periods (75% vs 70%). This difference disappeared when adjusting for age, meaning that the difference could be explained by higher age of the patients in the PCV10 period. In conclusion, no major changes in clinical characteristics of IPD patients were observed after introduction of PCV10 in 2011.

In the PRIEMA study (described in section 7.2.5) the immune response after the routine vaccination schedule was determined in order to explore whether the current schedule is optimal for premature babies. After preliminary analysis of the first 157 serum samples of the post-primary series at 5 months, the proportion with insufficient protective antibodies against pneumococci (< 0.35µg/ml) varied by serotype from 4% (serotype 7F) to 55% (serotype 6B). After the booster vaccination, this percentage of protection by sufficient antibody levels was much higher (91-100%).

In PCV13, all serotypes are conjugated to CRM197, a non-toxic mutant of diphtheria toxin, while in PCV10 most serotypes are conjugated to protein D (derived from non-typeable *Haemophilus influenza*); in PCV10 only serotype 18C is conjugated to tetanus toxoid carrier protein and serotype 19F is conjugated to diphtheria toxoid carrier protein. Previous studies found that maternal tetanus, diphtheria and acellular pertussis (Tdap) vaccination causes blunting of the infant's immune response to PCV13 because the diphtheria vaccination during pregnancy interferes with the immune response of the infants to the CRM-197 carrier protein [1, 2]. In an RIVM study on maternal pertussis vaccination, it was assessed whether maternal Tdap vaccination interferes with the infant's IgG response to PCV10, in which most serotypes are conjugated to protein D. IgG antibodies against pneumococcal vaccine polysaccharides conjugated to protein D were not significantly different between infants in the maternal vaccination group and control group. In contrast, antibodies against serotype 19F, which is conjugated to diphtheria toxoid, were significantly lower, both post-primary and post-booster vaccination, in infants in the maternal vaccination group compared with the control group. In conclusion, no blunting of antibody response against pneumococcal serotypes conjugated to protein D after maternal Tdap vaccination was observed.

Currently, there is no pneumococcal vaccination program for the elderly in the Netherlands. The impact and cost-effectiveness of vaccination with PPV23 versus PCV13 among those aged 60, 65 or 70 were assessed for the Netherlands in combination with replacing PCV10 with PCV13 in the infant vaccination programme [3]. Compared with the current vaccination with PCV10 for infants, the largest impact on pneumococcal disease burden was projected with a combined use of PCV13 among infants and PPV23 at 60, 65 and 70 years. The most cost-effective strategy was vaccinating with PPV23 at 70 years only with similar low ICERs at age 60 and 65. The impact of the use of PCV13 among infants depends strongly on the projected herd-immunity effect on serotype 19A. Vaccinating the elderly with either PCV13 or PPV23 was

dominated by PPV23 in all investigated scenarios, mainly due to the lower price of PPV23. Under current assumptions, the best value for money is the use of PPV23 for the elderly, with a single dose or a five-year increment between age 60 and age 70.

7.9.6 International developments

7.9.6.1 IPD

Rinta-Kokko et al. evaluated the long-term impact of PCV10 vaccination against IPD in children six years after PCV10 introduction in Finland [4]. The incidence of all IPD decreased by 79% (95% CI 74–83%) among vaccine-eligible children. There was a significant reduction in the incidence of 6A IPD, but for 19A IPD, the reduction was non-significant and the incidence of 19A IPD increased towards the end of the study period in the older vaccine-eligible children. In the unvaccinated older children, the incidence of all IPD decreased by 33% (95% CI 8–52%) and there was no impact on serotype 6A or 19A IPD. The data suggest that PCV10 results in long-lasting direct cross-protection against 6A IPD. For 19A, no net reduction was observed six years after PCV10 introduction in the vaccine-eligible cohort.

Ladhani et al. described the impact of PCV7 and PCV13 on IPD in England and Wales using national IPD surveillance data [5]. They compared incidence rates for 2016/17 with rates pre-PCV13 (2008/09–2009/10) and pre-PCV7 (2000/01–2005/06). In 2016/17, overall IPD incidence across all age groups was 37% lower than pre-PCV7 incidence, and 7% lower than pre-PCV13 incidence. By 2016/17, PCV7-type IPD incidence across all age groups had decreased by 97% compared with the pre-PCV7 period, whereas additional PCV13-type IPD decreased by 64% since the introduction of PCV13. IPD incidence due to non-PCV13 serotypes doubled since the introduction of PCV7, and has accelerated since 2013/14—especially serotypes 8, 12F, and 9N, which were responsible for more than 40% of IPD cases by 2016/17. In conclusion, both PCV7 and PCV13 have had a major effect in reducing the burden of IPD in England and Wales; however, rapid increases in some non-PCV13 serotypes are compromising the programme's benefits.

Naucler et al. compared the impact of PCV10 and PCV13 on IPD in Sweden, where the 21 counties use either PCV10 or PCV13 [6]. The impact on overall IPD was not significantly different between the two vaccines (23% reduction for PCV10 and 29% reduction for PCV13). Moreover, in the different age groups, no differences were found between the vaccines in overall impact.

Makwana et al. describe characteristics of children with IPD in England and Wales for the period 2010–2016 [7]. A total of 1255 children were included. Overall, 259 (21%) children had comorbidities, particularly immunosuppression (32%). The case fatality rate was 5.1% (64/1255) and independently associated with meningitis (aOR 3.53; 95% CI: 1.62–7.70) and presence of comorbidity (aOR, 2.41; 95% CI: 1.25–4.64). In 2015/2016, PCV13 serotypes were responsible for 10.8% (25/232) of serotyped cases; the most prevalent non-PCV13 serotypes were 12F (18%), 10A (12%), 23B (10%), 33F (10%), 15B/C (10%) and 8 (8%).

7.9.6.2 *Pneumonia*

McLaughlin et al. used a test-negative design to estimate the VE of PCV13 in US adults aged ≥65 years against vaccine-type community-acquired pneumonia (CAP) [8]. Cases were defined as hospitalised CAP patients, with PCV13 serotypes identified via culture or serotype-specific urinary antigen detection assay. Remaining CAP patients served as test-negative controls. Of 2034 CAP hospitalisations, PCV13 serotypes were identified in 68 (3.3%). Cases were less likely to have received PCV13 than controls (3/68 [4.4%] vs 285/1966 [14.5%]; unadjusted VE, 72.8% [95% confidence interval, 12.8%–91.5%]). No confounding was observed during adjustment for patient characteristics, including immunocompromised status, body mass index, and history of influenza and pneumococcal polysaccharide vaccination (adjusted VE range, 71.1%–73.3%).

7.9.6.3 *Immunogenicity*

Goldblatt et al. compared the post-booster antibody response of a 1+1 schedule (3 and 12 months of age) versus a 2+1 schedule (2, 4 and 12 months of age) in 213 UK infants in a randomised controlled trial [9]. For nine of the 13 serotypes in PCV13, post-booster responses in infants primed with a single dose were equivalent or superior to those seen following a 2+1 schedule. Introducing a 1+1 schedule in countries with a mature PCV programme and established herd immunity is likely to maintain population control of vaccine-type pneumococcal disease.

7.9.6.4 *Carriage*

Van Deursen et al. investigated the direct effects of PCV13 on nasopharyngeal carriage by PCR in older adults living at home, as part of the CAPiTA study [10]. Before randomisation, 339 of 1891 subjects had nasopharyngeal carriage with any pneumococci (17.9%), and 114 of 1891 (6.0%) carried vaccine type (VT) pneumococci. At 6 months after vaccination, VT pneumococcal carriage was significantly lower in PCV13 recipients than in the placebo group. There was no difference between the groups at 12 and 24 months after vaccination. Carriage of non-VT pneumococci, *S. aureus*, *H. influenzae*, and *M. catarrhalis* did not differ between groups.

7.9.6.5 *Antibiotic use*

A population-based cohort study in Dutch infants assessed the impact of switching from PCV7 to PCV10 on outpatient antibiotic use [11].
Anonymised antibiotic purchase data of 255,154 Dutch infants aged under 2 years from Achmea Health were extracted for the period 2006-2013. PCV10 introduction was associated with a modest 1.6% overall reduction in antibiotic use (purchase rate ratio: 0.98, 95% CI: 0.98 to 0.99). The model showed a significant difference in time trend in antibiotic use after PCV10 introduction (p=0.0084) with an increase in prescriptions in the PCV7 period (slope: 0.0023/month, 95% CI: −0.0001 to 0.0047) versus a decline in the PCV10 period (slope: −0.0089/month, 95% CI: −0.0150 to −0.0029). Switching from PCV7 to PCV10 was associated with a modest decline in outpatient antibiotic use in Dutch infants.

7.9.6.6 *Cost-effectiveness*

Since 2005, vaccination with PPV23 has been included in the Australian National Immunisation Program (NIP) for persons aged >65 years and other risk groups. Vaccination coverage was

around 60%. In 2016, the vaccine was replaced by a single dose PCV13. In an economic evaluation, the ICER for the PCV13 program compared to no vaccination was AUS $88,100 per QALY gained [12]. The cost-effectiveness of PCV13 in comparison to PPV23 was AUS $35,300 per QALY gained.

In 2014, the Belgian Health Council recommended primary vaccination with PCV13, followed by PPV23 after at least 8 weeks for all adults aged 65–85. However, the uptake of pneumococcal vaccines remains low in adults, which could also be due to a lack of reimbursement. The cost-effectiveness of PPV23 and/or PCV13 was compared with the 2016 situation considering a low PPV23 vaccination coverage [13]. A strong preference for PPV23 over PCV13 in all age groups was found. PPV23 vaccination would cost on average about €83,000, €60,000 and €52,000 per QALY gained in 50–64, 65–74 and 75–84 year olds, whereas for PCV13 this is about €171,000, €201,000 and €338,000, respectively.

The cost-effectiveness of no vaccination compared with vaccination with PCV10 and PCV13 was assessed for newborns in Italy [14]. The incremental cost-effectiveness ratio (ICER) for PCV10 was €50,000 per QALY gained, and for PCV13 it was €55,000 per QALY gained. The authors concluded that compared with PCV13, PCV10 would provide better health outcomes and reduce costs because of its presumed differential effect on the incidence of non-typeable *Haemophilus influenzae* (NTHi) and acute otitis media (AOM) as in PCV10, most serotypes are conjugated to protein D derived from NTHi. Furthermore, f the cost-effectiveness of PCV10 compared to PCV13 for universal childhood immunisation was estimated for New Zealand [15]. The model estimated that both vaccines have a broadly comparable impact on IPD-related diseases and pneumonia. Due to the presumed additional benefits through broader impact on AOM, PCV10 is preferable to PCV13.

7.9.7 Literature

7.9.7.1 References

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7.10 Poliomyelitis

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

7.10.1 Key points

- In 2017 and in 2018 up to July 1, no cases of poliomyelitis were reported.
- In 2017-2018, polio remained endemic in three countries – Afghanistan, Nigeria and Pakistan.
- Worldwide, the number of circulating vaccine derived poliovirus (VDPV) increased in 2017 (158) compared with 2016 (8).
- From March to October 2017, there was a large outbreak of cVDPV2 in Syria.
- A large outbreak of VDPV2 in the Democratic Republic of the Congo (DRC) started mid-2017 and continued in 2018, threatening the polio eradication efforts.
- Following a vaccine trial in Antwerp, Belgium in May 2017, 5 participants left containment and returned to the Netherlands without confirmation by the Belgian researchers that their shedding of new OPV2 (nOPV2) was stopped. Containment measures were taken for those participants. Close monitoring revealed no threat to Dutch Public Health, and shedding stopped.

7.10.2 Tables and figures

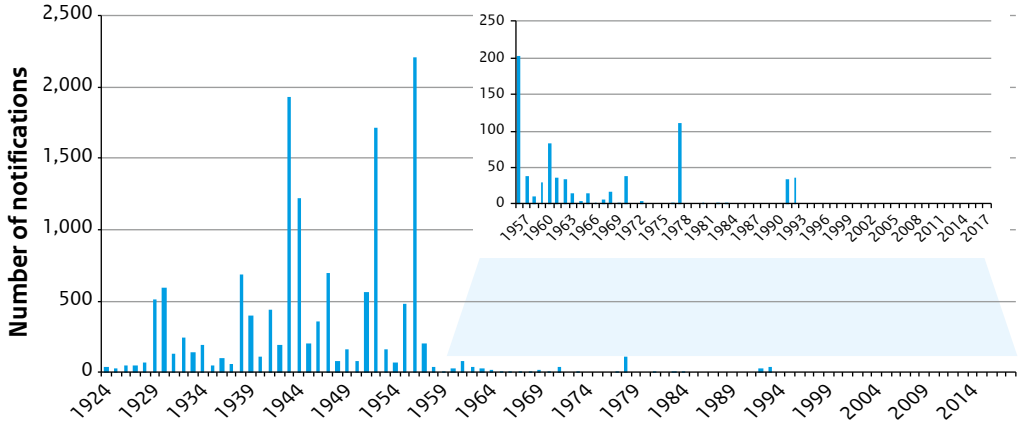

Figure 7.10.1 Notifications of poliomyelitis in the Netherlands from 1924-1956 (left part) and 1957-2018* (right part)
For 2018, reports up to July 1 are included

7.10.3 Epidemiology

In 2017 and in 2018 up to July 1, no cases of poliomyelitis were reported in the Netherlands. (Figure 7.10.1)

7.10.4 Pathogen

Following a vaccine trial in Antwerp, Belgium in May 2017, 5 participants for who shedding of new OPV2 (nOPV2) was not shown to have stopped, were allowed to leave containment and return to the Netherlands. For 4 of these participants, no shedding of nOPV2 virus was found in the Netherlands, but one participant continued shedding nOPV2 virus for 24 days while living in the Netherlands. The National Polio Laboratory (NPL) analysed 114 stool samples and one sewage sample for the presence of poliovirus. At the end of shedding, the VP1 of the nOPV2 strain had 5 mutations; none of the mutations responsible for reversion to pathogenicity were found.

From March to October 2017, there was a large outbreak of cVDPV2 in Syria. The NPL- RIVM, as reference laboratory for Turkey, sequenced over 200 poliovirus strains. 163 samples were cVDPV2 strains that belonged to this outbreak. The number of mutations varied between 23 and 34 nt. A total of 74 cases were identified, with the last case with onset of paralysis confirmed on September 21, 2017.

Mid-2017, a large outbreak of three different VDPV2 strains spread in the Democratic Republic of the Congo (DRC). The outbreak continues. The DRC government declared cVDPV2 to be a national public health emergency.

7.10.5 Research

The National Polio Laboratory (NPL) at the RIVM participates in several projects of the WHO Global Polio Laboratory Network (GPLN), including development of sensitive methods for direct poliovirus detection in clinical samples and the feasibility of Next Generation Sequencing methods to detect poliovirus sequences in sewage samples. Additionally, the NPL is developing an Environmental Surveillance Quality Assurance program to support the GPLN and the Environmental Surveillance expansion plan. New serological assays are developed that can be used outside of GAPIII containment. One of the assays is a new anti-PV IgA assay that will prove valuable in the future as it will enable sensitive screening for mucosal contact with infectious polioviruses. After complete WPV eradication (for all three types), it is anticipated that use of OPV will be ceased.

7.10.6 International developments

In 2017-2018, polio remained endemic in three countries – Afghanistan, Nigeria, and Pakistan. In 2017 and 2018 up to July 1, no importation of polio in non-endemic countries was observed. Currently only WPV1 is circulating, as WPV2 and WPV3 stopped circulating in 1999 and 2014, respectively.
The number of circulating vaccine derived poliovirus (VDPV) increased in 2017 (158) compared with 2016 (8). Forty-three VDPVs have been reported in 2018 up to August 28. To boost a further reduction in VDPVs before June 2016, all countries with oral polio vaccine (OPV) in their

immunisation programme, switched from trivalent OPV to bivalent OPV which does not contain poliovirus type 2. To comply with the WHO global action plan for poliovirus containment (GAPIII), all materials containing poliovirus type 2 should be destroyed or contained in poliovirus essential facilities (PEFs). In the Netherlands, the inventory of facilities maintaining poliovirus materials yielded 7-9 would be PEFs.
To strengthen protection through vaccination, WHO advised that all countries include at least one dose of inactivated polio vaccine (IPV) in their immunisation programme from 2015 onwards.
Unfortunately due to IPV shortage, not all countries have managed to implement this to date.

7.10.6.1 Vaccines

The WHO prequalified a new bivalent oral polio vaccine (bOPV) developed by Chinese vaccine manufacturer Beijing Bio-Institute Biological Products (BBIBP), helping high risk countries to gain access to a cheaper version of the vaccine.

7.10.7 Literature

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* RIVM publication

7.11 Rubella

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7.11.1 Key points

- In 2017 and the first six months of 2018, no cases of rubella were reported.

7.11.2 Tables and figures

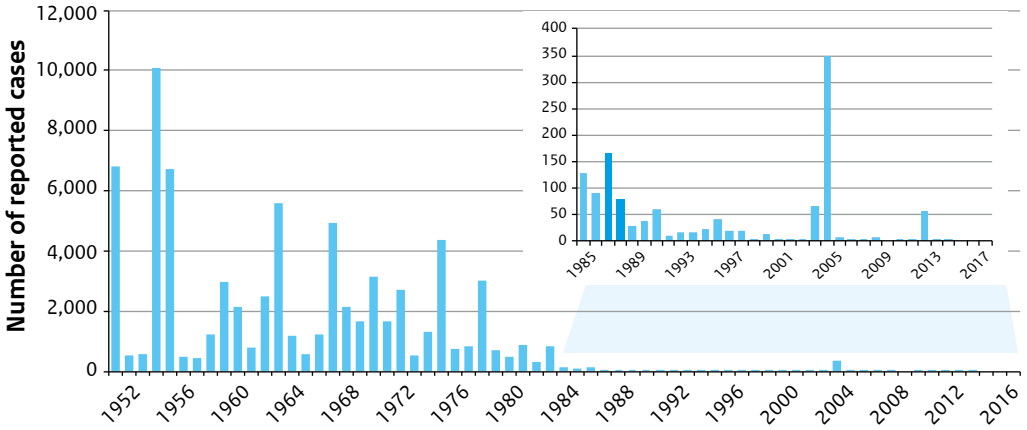

Figure 7.11.1 Annual reported rubella cases since 1952

7.11.3 Epidemiology

In the calendar year 2017 and in the first half of 2018, no rubella cases were reported (Figure 7.11.1). The last outbreak took place in 2004-2005 in the so-called 'Bible Belt', in which almost 400 cases were reported [1]. In 2013, a small outbreak around an orthodox protestant school, with over 50 cases. In 2014 to 2016, three cases were reported.

7.11.4 Research

7.11.4.1 Seroepidemiological study among asylum seekers

To assess the level of protection against nine vaccine preventable diseases, we conducted a seroprevalence study among refugees aged 18-45. In 2016, over 600 refugees from Syria, Afghanistan, Iraq, Iran and Eritrea living in three large asylum seeker centres participated in the study [2]. The overall seroprevalence against rubella was high with 94%, and ranged from 84% in Iraq to 98% in Syria and Eritrea. The prevalence in participating women was 92%. In the Netherlands, pregnant asylum seekers are screened for rubella and varicella [3].

7.11.5 International developments

Since the large rubella outbreak in Poland with over 38,000 cases reported in 2013, the number of cases in Europe has continued to decline. In 2017, 11 EU/EEA countries reported 696 rubella cases, of which 496 (71%) were from Poland [4]. Other countries reporting significant numbers of rubella in 2017 were Germany (73 cases) and Italy (67 cases). Seventeen EU/EEA countries reported zero cases of rubella in 2017 [4]. Up to June 2018, sporadic cases were reported across EU/EEA countries, but no outbreaks have been detected [5]. WHO has finalised and launched their 3rd edition of the Laboratory manual for measles and rubella surveillance [6].

7.11.6 Literature

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* RIVM publication

7.12 Tetanus

N.A.T. van der Maas, D.W. Notermans, H.E. de Melker

7.12.1 Key points

- In 2017, one case of tetanus was reported. No cases were reported in 2018, up to July 1.

7.12.2 Tables and figures

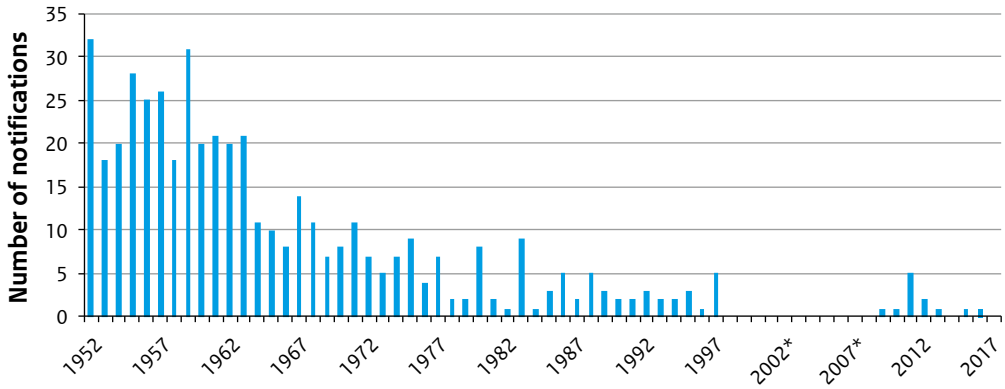

Figure 7.12.1 Reported cases of tetanus in the Netherlands by year, 1952-2018^
* Between 1999 and 2009 tetanus was not notifiable.
^ For 2018, notifications up to July 1st were counted.

7.12.3 Epidemiology

In 2017, an elderly woman with unknown vaccination status with signs of tetanus was hospitalised and reported. Her birth cohort was not eligible for routine vaccination and on admission, according to LCI guidelines she should have been offered Tetanus Toxoid and anti Tetanus Immunoglobulines, but she only received Tetanus Toxoid as post-exposure prophylaxis. In the first half of 2018, no cases of tetanus were reported.

7.12.4 Pathogen

One isolate of *Clostridium tetani* was submitted and tested positive for PCR toxin gen testing. This infection did not cause any symptoms, so the person was not notified with tetanus. *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.

8
The immunisation programme in Caribbean Netherlands

J. van Slobbe, K. Hulshof, R.A. Vos, J. Hubert, A. Janga-Jansen, M. Wijsman, S. Baboe-Kalpoe, D. Abraham, E. Maduro, F. Rooyer, M. Kuppenvelt, H. van den Kerkhof

8.1 Key points

- In general, vaccination coverage in the Caribbean Netherlands is high.
- In Bonaire, at the end of 2016 and the beginning of 2017 (over a period of about 6 months), some cases of whooping cough were reported, and in 2013 a case of Hib. In recent years an average of two cases with hepatitis B have been reported every year.
- In Saba, no cases of diseases included in the NIP were diagnosed in 2017.
- From 2013 up to 2017 in Aruba, 272 reports of vaccine preventable diseases (VPDs) were received, most of which concerned hepatitis B infection (64.0%).
- From May-June 2017, sampling for the Health Study Caribbean Netherlands (HSCN) was conducted on the Dutch Caribbean Islands of Bonaire, St. Eustatius and Saba. Overall, 1,900 people were enrolled in the study, of which 1,197 (26%) on Bonaire, 480 (23%) on St. Eustatius, and 223 (22%) on Saba. First results indicate overall seroprevalences of 94% for measles, 85% for mumps, 85% for rubella, 78% for varicella, 78% for diphtheria, 10% for pertussis and 99% for tetanus.

8.2 Tables and figures

Table 8.1 Vaccination coverage[a,b] in Caribbean Netherlands

	Aruba	Bonaire	St. Eustatius	Saba
Newborns (2 years)				
Number in cohort 2015	1,271	[d] 168	33	20
Number DTaP-IPV-Hib-HBV	1,170	156	32	20
% DTaP-IPV-Hib-HBV	92.1	92.9	97.0	100
Number PCV	1,171	155	32	20
% PCV	[c] 92.1	92.3	97.0	100
Number MMR	1,211	145	32	20
% MMR	95.3	90.1	97.0	100
Number MenC		145	32	20
% MenC		90.1	97.0	100

	Aruba	Bonaire	St. Eustatius	Saba
Toddlers (5 years)				
Number in cohort 2012	1,392	233	34	16
Number DT(aP)-IPV	1,007	202	29	16
% DT(aP)-IPV	72.3	86.7	[e] 85.3	100
Number MMR	981	-	29	-
% MMR	70.5	-	85.3	-
Schoolchildren (10 years)				
Number in cohort 2007	1,495	233	40	13
Number DTP	1,400	126	39	13
% DTP	[f] 93.6	[g] 54.1	97.5	100
Number MMR	1,409	156		13
% MMR	[f] 94.2	[g] 67.0		100
Adolescent girls (10 years)				
Number in cohort 2007	744	115	17	<10
Number HPV	365	12	15	<10
% HPV	[f] 49.1	[h] 10.4	88.2	100

[a] The registration systems in Caribbean Netherlands are not connected to the national population register, therefore, children who have emigrated to neighbouring islands or elsewhere may be included in the denominator (the total number of children), but not in the numerator (the number of vaccinated children). The vaccination coverage can therefore in reality be higher than shown. For Bonaire, the data from birth cohort 2012 are linked ad hoc to the population administration.

[b] Vaccination status at two years of age: DTaP-IPV/MMR = basic immunity, Hib/HBV/PCV/MenC = completely closed; at age five: DT(aP)-IPV = re-vaccinated; at the age of ten: DTaP/MMR/HPV = full participation.

[c] In 2016 there was a shortage of PCV, as a result of which many PCV3 vaccinations were postponed (and possibly adjusted).

[d] Due to moving abroad, the number of children in the 2015 cohort for the MMR and MenC vaccination was lower, namely 161.

[e] On St. Eustatius, four-year-olds received DTaP instead of DTaP-IPV up to and including 2015.

[f] For Aruba, it was not possible to calculate the vaccination rate for cohort 2007 at the age of ten. In Aruba, schoolchildren and adolescent girls are vaccinated per class (at different ages). For Aruba, therefore, the numbers and percentages for school year 2016/2017 (group 7 for schoolchildren and group 8 for adolescent girls) are shown, regardless of the age of the children.

[g] Interim vaccination coverage: the vaccination for nine-year olds is linked to school year and not to birth year. For girls, there are two vaccination moments (9 years: HPV1 + MMR and 9.5 years: HPV2 + DTaP), hence the percentage for MMR is higher than for DTaP. Cohort 2007 was again invited in June 2018 (girls: HPV2 + DTaP and boys MMR + DTaP). There will also be a campaign with extra attention for school vaccination.

[h] Interim vaccination coverage: in June 2018, these girls are called up for HPV2 (40.9% have received HPV1). A number of parents also indicated that they only want their daughter to be vaccinated at the age of thirteen (as in the Netherlands).

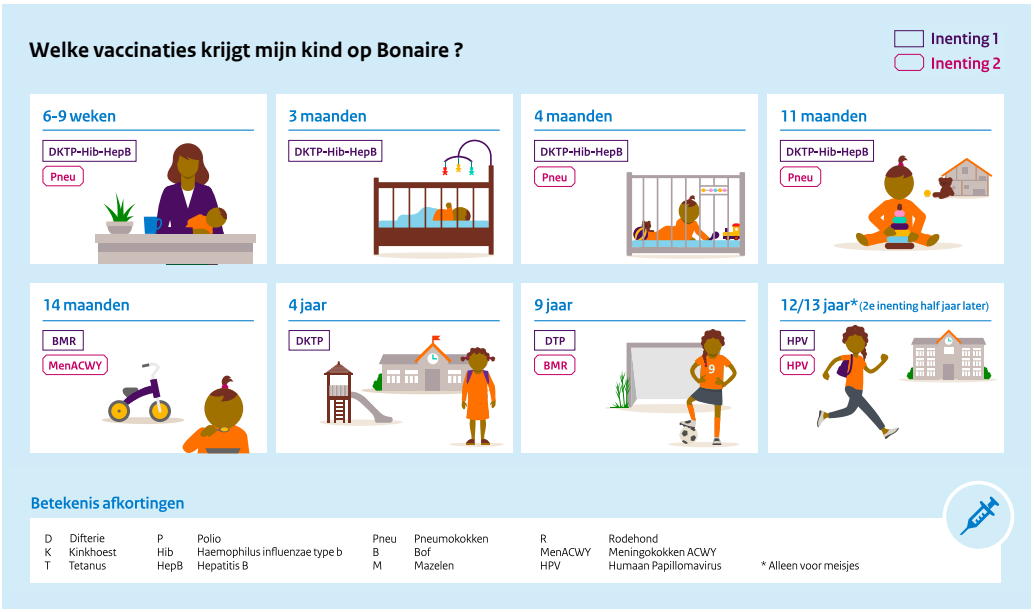

Figure 8.1 Immunisation schedule for Bonaire (in Dutch)

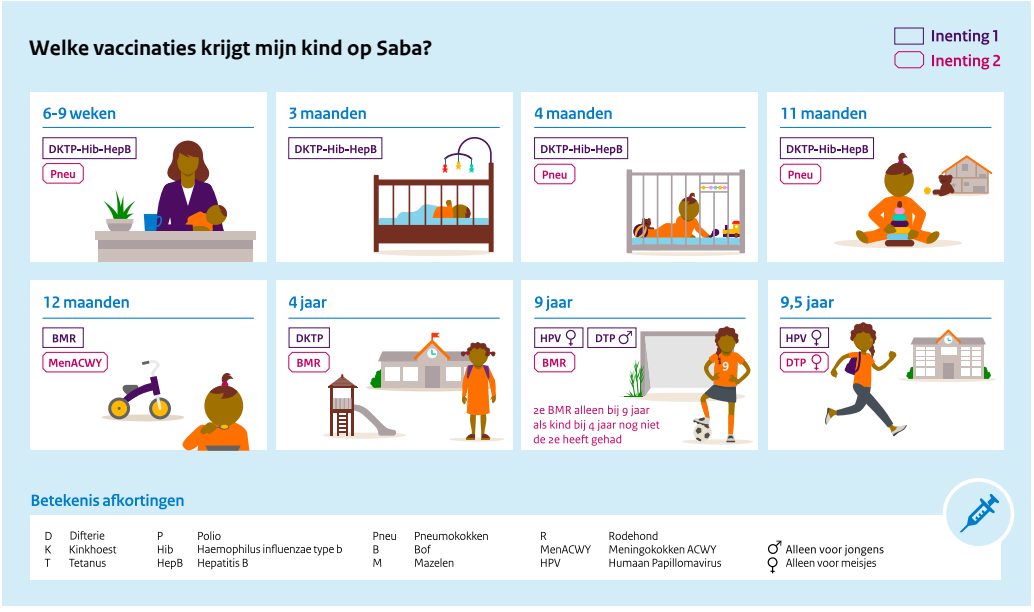

Figure 8.2 Immunisation schedule for Saba (in Dutch)

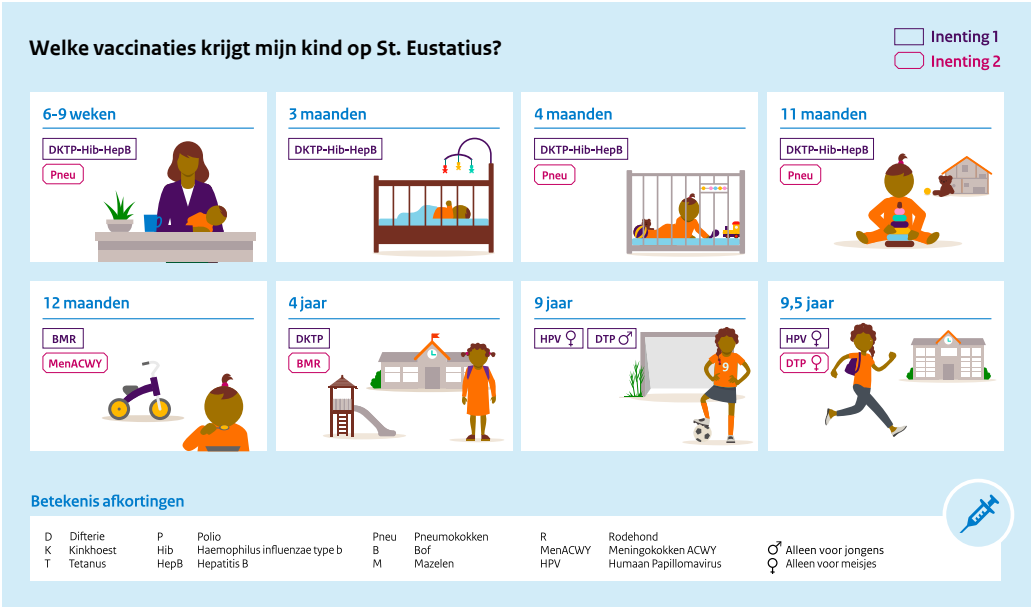

Figure 8.3 Immunisation schedule for St. Eustatius (in Dutch)

Fase 1	Inenting 1	Inenting 2
1 maand	HepB	
2 maanden	DKTP Hib	Pneu
3 maanden	HepB	
4 maanden	DKTP Hib	Pneu
6 maanden	DKTP Hib	
9 maanden	HepB	
12 maanden	BMR	Pneu
15 maanden	DKTP Hib	

Fase 2	Inenting 1	Inenting 2
4 jaar	DKTP	BMR

Fase 3	Inenting 1	Inenting 2
Groep 7	DKTP	

Fase 4	Inenting 1	Inenting 2
Groep 8	HPV*	HPV* (na 6 mnd)

Betekenis afkortingen

D	Difterie
K	Kinkhoest
T	Tetanus
P	Polio
Hib	Heamophilus influenza type b
HepB	Hepatitus B
Pneu	Pneumokokken
B	Bof
M	Mazelen
R	Rode hond
HPV	Humaan Papillomavirus
*	Alleen voor Meisjes

Figure 8.4 Immunisation schedule for Aruba (in Dutch)

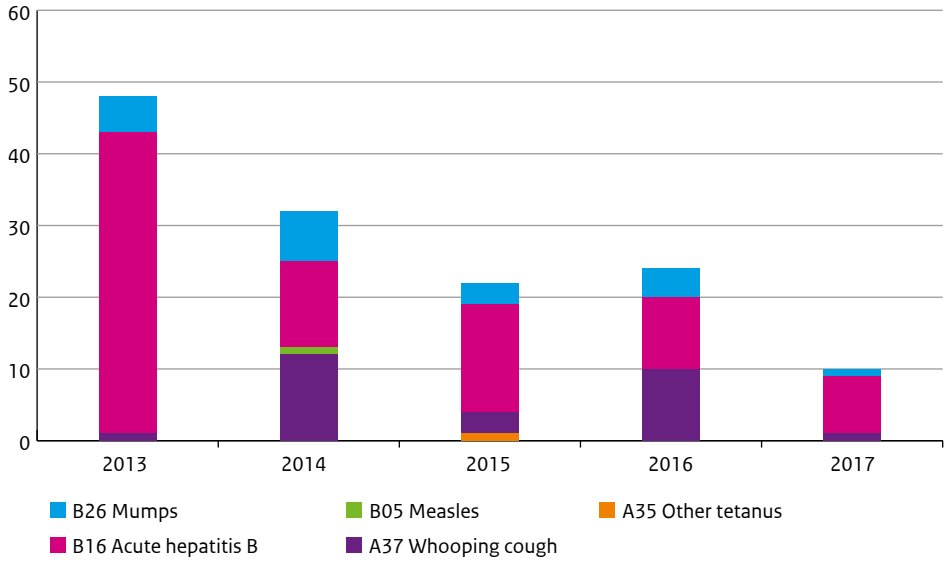

Figure 8.5 Reported Vaccine Preventable Diseases, Aruba 2013-2017

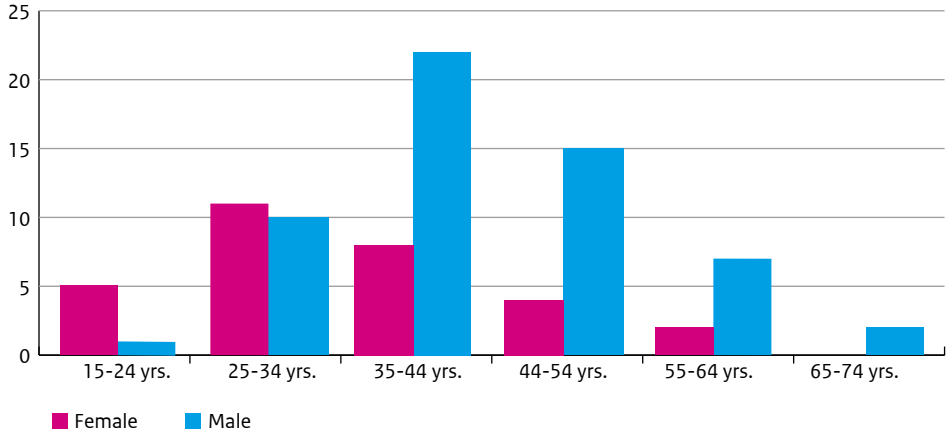

Figure 8.6 HBV infection by age category and gender, Aruba 2013-2017

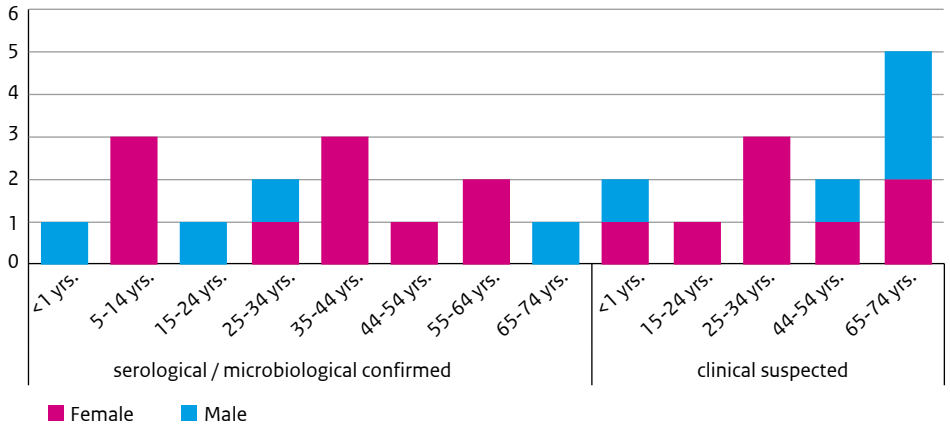

Figure 8.7 Confirmed/ clinical suspected Whooping cough cases by age category and gender, Aruba 2013-2017

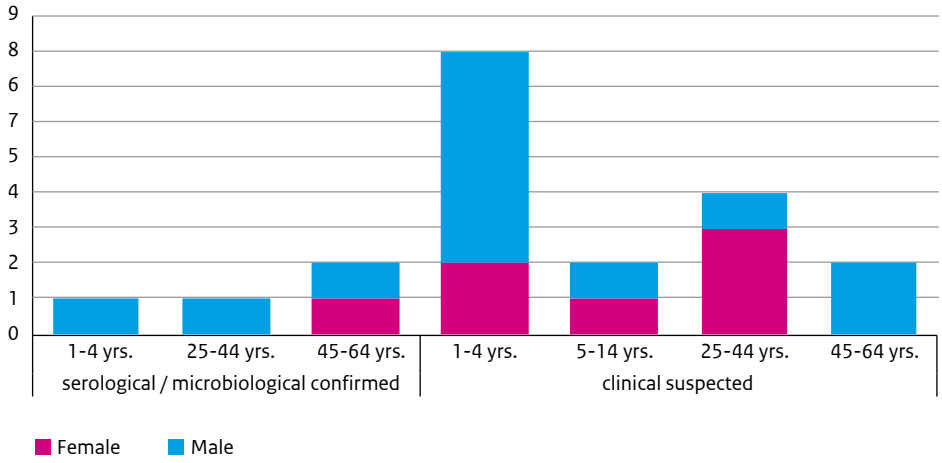

Figure 8.8 Confirmed/ clinical suspected mumps cases by age category and gender, Aruba 2013-2017

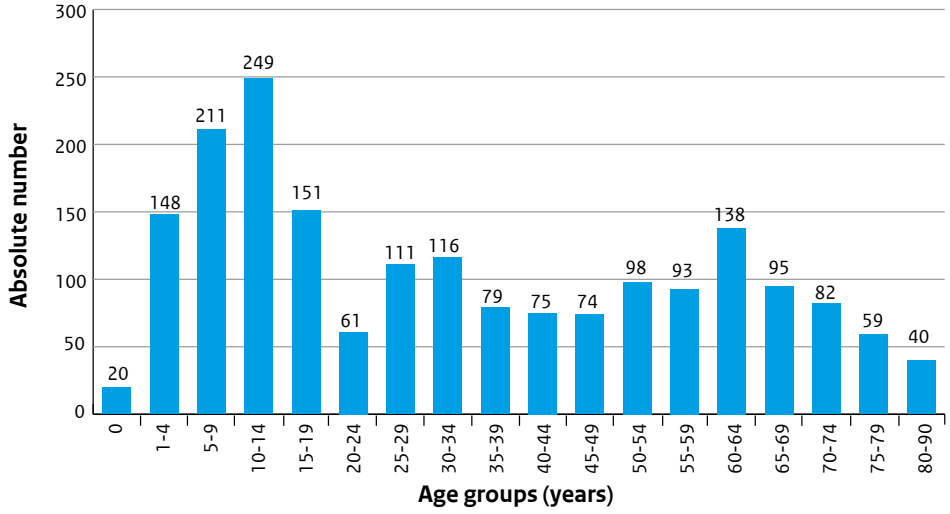

Figure 8.9 Absolute number of participants in the HSCN (N_{total} = 1,900), per age group

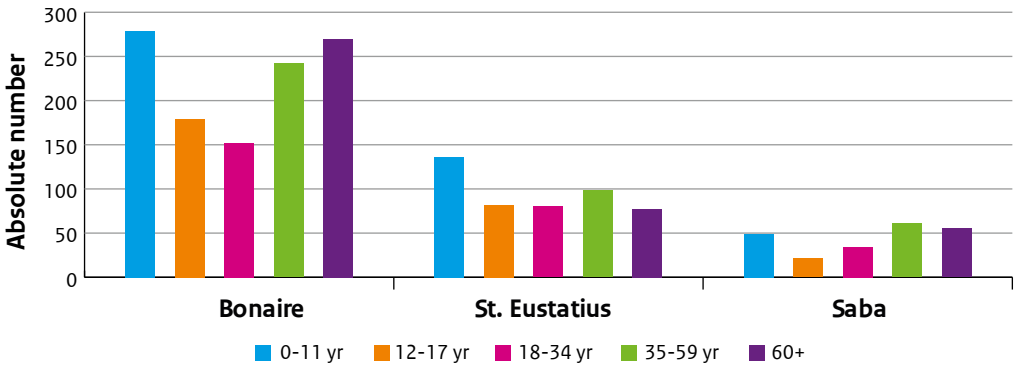

Figure 8.10 Absolute number of participants in the HSCN who donated a blood sample and completed the risk factor questionnaire (N_{total} = 1,815), per island and age stratum

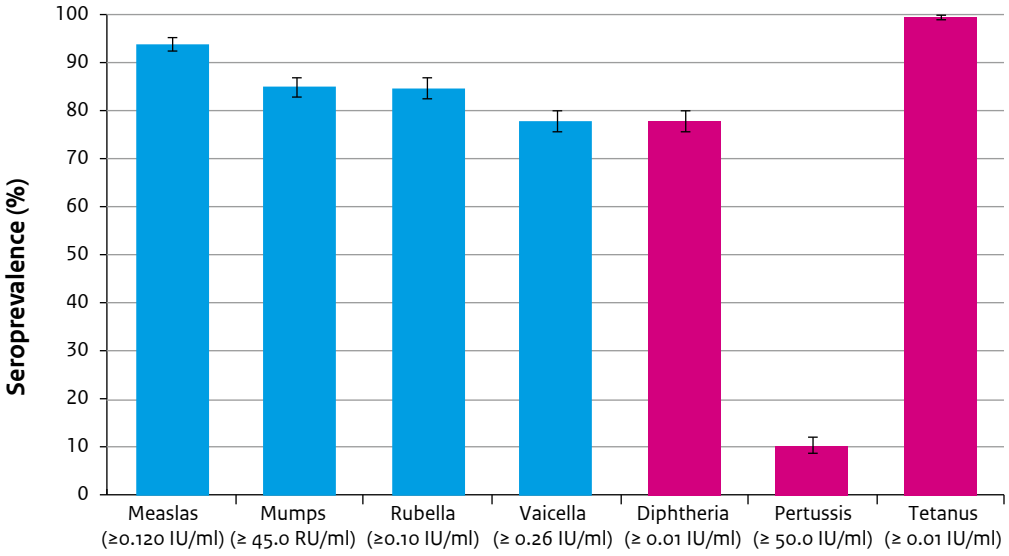

Figure 8.11 Weighted overall seroprevalence (with 95% confidence intervals) of measles, mumps, rubella and varicella (blue), and diphtheria, pertussis and tetanus (orange) IgG antibodies in the general population of Caribbean Netherlands (N_{total} = 1,829). Note: cut-off for seropositivity in parentheses

8.3 Immunisation schedules

Immunisation schedules in Caribbean Netherlands are presented in Figures 8.1-8.4. Bonaire has, in accordance with European Netherlands, switched the MenC vaccine to the MenACWY vaccine as of 1 May 2018.

8.4 Vaccination coverage

Table 8.1 presents vaccination coverage in the Caribbean Netherlands. In general, vaccination coverage is high. For Curaçao and St. Maarten, no data on vaccination coverage could be included this year due to logistical and research technical reasons.
The method for determining vaccination coverage, as used in this section, often gives an underestimation for school-aged children in this area, because vaccinations are usually offered per school year, regardless of the birth year of a child. The age limits of five and ten years were not always met in that case. Compared to last year, for example, the vaccination coverage for children born in 2006 on Saba has increased from 86% to 100%.

8.5 Epidemiology of diseases included in the NIP

8.5.1 Epidemiology in Bonaire

At the end of 2016 and the beginning of 2017 (over a period of about 6 months), some cases of whooping cough were reported including two neonates (3 and 6 weeks old), an unvaccinated 1-year-old, and 6 adults.
In 2013, a case of Hib was reported in an unvaccinated 1-year-old.
An average of two cases (almost always adults) with hepatitis B have been reported every year in recent years; these are often people from other countries.

8.5.2 Epidemiology in Saba

No cases of NIP diseases were diagnosed in 2017.

8.5.3 Epidemiology in St. Eustatius

Data on the epidemiology of VPDs in St. Eustatius will be reported next year.

8.5.4 Epidemiology in Aruba

From 2013 up to 2017, the Epidemiology and Research Unit of the Department of Public Health Aruba (DPHA) received 272 reported Vaccine Preventable Diseases (VPD), of which most were Hepatitis B (HBV) infection (64.0%). Figure 8.5 gives an overview of the reported VPDs. More males compared to females were reported with a VPD (58.8% versus 41.2%). In addition, most of these VPDs were people in the age category 25-44 (47.1%). Please note that 13.2% were children aged 0-14.

8.5.4.1 Hepatitis B infection

There is a decline in serological confirmed cases of HBV infection; 8 confirmed cases in 2017 compared to 42 in 2013. Analysis by age category and gender shows more males aged 35 and older had an HBV infection. In contrast, more females aged 15 - 34 had an HBV infection compared to males of the same age (figure 8.6).

8.5.4.2 Whooping cough

Health care givers reported 27 whooping cough cases in the period 2013 - 2017, with an increase in notifications in 2014 and 2016. Confirmed and clinically suspected cases were almost equal. Two-thirds of the whooping cough were reported by females. Figure 8.7 gives an overview of whooping cough cases by type of diagnosis, by age category, and by gender.

8.5.4.3 Mumps

The DPHA Epidemiology and Research Unit received 20 mumps cases notifications in the period 2013 - 2017, of which one in five was a laboratory confirmed mumps infection (Figure 8.8). Of the four confirmed cases, one was a vaccinated one-year-old male. Clinically suspected mumps cases remain high due to the lack of a second blood sample required for confirmation.

8.5.4.4 Other

The other two vaccine preventable diseases, Tetanus and Measles, were clinically suspected cases.

8.5.5 Epidemiology in Curaçao

Data on the epidemiology of VPDs in Curaçao will be reported next year.

8.5.6 Epidemiology in St. Maarten

Data on the epidemiology of VPDs in St. Maarten will be reported next year.

8.6 Research

8.6.1 Health Study Caribbean Netherlands

From May-June 2017, the PIENTER survey has been extended to include the Dutch Caribbean Islands of Bonaire, St. Eustatius and Saba. In this Health Study Caribbean Netherlands (HSCN), RIVM partnered with Statistics Netherlands (CBS) and local Public Health departments (GGD) on the islands. The main goal was to assess how well the population of the islands is protected against infectious diseases. In addition, this study looked at a wider-range than the Dutch PIENTER version, as it aimed at investigating both lifestyle and chronic illness ('Volksgezondheid Toekomst Verkenning' (VTV)). The results will be shared with the islands in order to support public health policy in the Caribbean Netherlands, in order to more effectively prevent and control illness in the future.

An age-specific sampling technique was used to draw a representative sample of the population (Ntotal=8,068: Bonaire: 4,798; St. Eustatius: 2,135; and Saba: 1,135). Age strata were 0-11, 12-17, 18-34, 35-59 and 60-90. Participants were invited by mail to visit a community centre in their neighbourhood to take part. Promotional efforts prior to and during the survey were applied to increase inclusion. The study involved testing blood samples to detect antibodies in order to obtain insights into the age-specific seroprevalence of (candidate) NIP-targeted diseases, as well as local tropical pathogens in the Dutch Caribbean population. Additionally, naso- and oropharyngeal swabs samples were taken to investigate presence of bacteria and viruses in the nose and throat. Stool samples were collected in order to analyse the microbiome of the gut and to investigate antibiotic resistance. Finally, height, weight and blood pressure were measured, and the participants were asked to complete a questionnaire about risk factors, lifestyle and chronic illness.

Of the invited population, 7,768 people (96.3%) met the inclusion criteria. 1,900 people (24%) participated in the study (45% males), of which 1,197 (26%) on Bonaire, 480 (23%) on St. Eustatius, and 223 (22%) on Saba. Total inclusion of the HSCN per age groups is shown in Figure 8.9. In total, 1,829 (96%) donated a blood sample and 1,885 (99%) completed the questionnaire. Figure 8.10 shows inclusion per island and age stratum regarding the collection of a blood sample in combination with a questionnaire. Samples of nasophayngeal swabs, oropharyngeal swabs and faeces were collected from 1,752 (92%), 1,502 (79%), and 1,547 (81%), respectively, and 1,515 (80%) donated all materials. Vaccination status was retrieved from 974 (51%) participants and 1,762 (93%) gave consent to be approached for a potential follow-up study.

First results regarding the general Dutch Caribbean population (Figure 8.11) indicate that the weighted overall seroprevalence of measles IgG antibodies was 93.8% (cut-off for seropositivity ≥ 0.120 international units (IU)/ml); of mumps 85.0% (≥ 45.0 RIVM units/ml); of rubella 84.5% (≥ 10.0 IU/ml); of varicella 78.0% (≥ 0.26 IU/ml); of diphtheria 78.0% (≥ 0.01 IU/ml); of pertussis 10.3% (≥ 50.0 IU/ml was used as a cut-off for pertussis infection in the preceding year); and of tetanus 99.5% (≥ 0.01 IU/ml). Currently, epidemiological analyses are being conducted to assess risk factors for seronegativity for these diseases, and results are expected in the course of 2018 and 2019. Likewise, results concerning the other laboratory analyses are anticipated for 2019 and 2020.

9
Future NIP candidates

9.1 Hepatitis A

I.H.M. Friesema, A.W.M. Suijkerbuijk, W. Luytjes, H. Vennema

9.1.1 Key points

- In 2017, the number of reported hepatitis A patients increased sharply to 374 cases compared to previous years (2011-2016: 80-125 cases).
- An international outbreak of hepatitis A among MSM, ongoing since July 2016, caused the significant increase of cases with 243 outbreak-related cases in 2017 in the Netherlands.
- For every two MSM cases, one person from the general population was infected with the outbreak strain.
- 92 cases of the remaining patients were unrelated to this outbreak and 39 cases could not be assigned, as no strain information was available and no direct epidemiological link to another case was reported.

9.1.2 Tables and figures

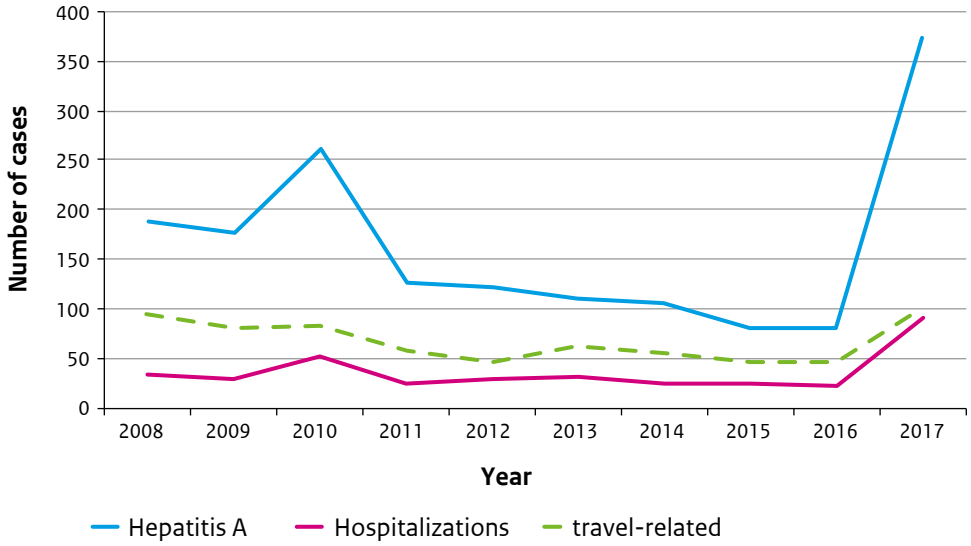

Figure 9.1.1 Number of reported, hospitalised and travel-related cases of hepatitis A, 2008-2017
Source: Osiris

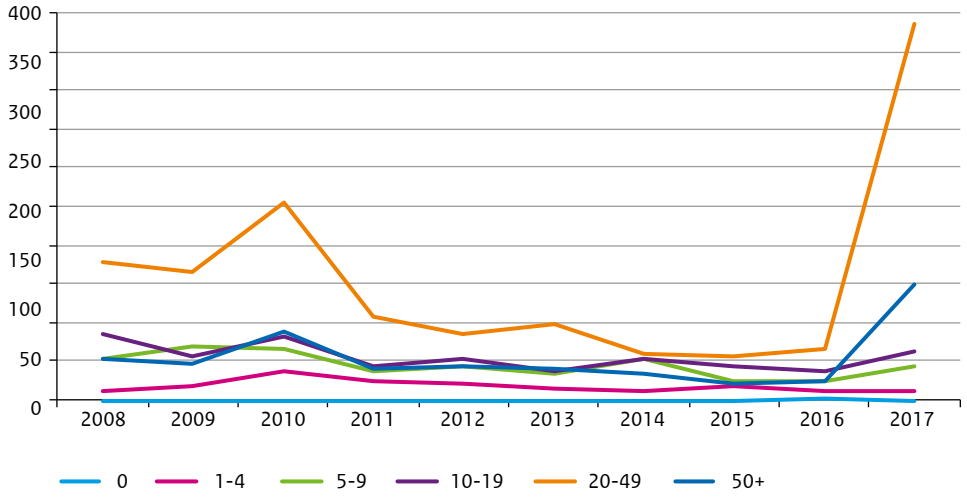

Figure 9.1.2 Age distribution of hepatitis A-cases, 2008-2017
Source: Osiris

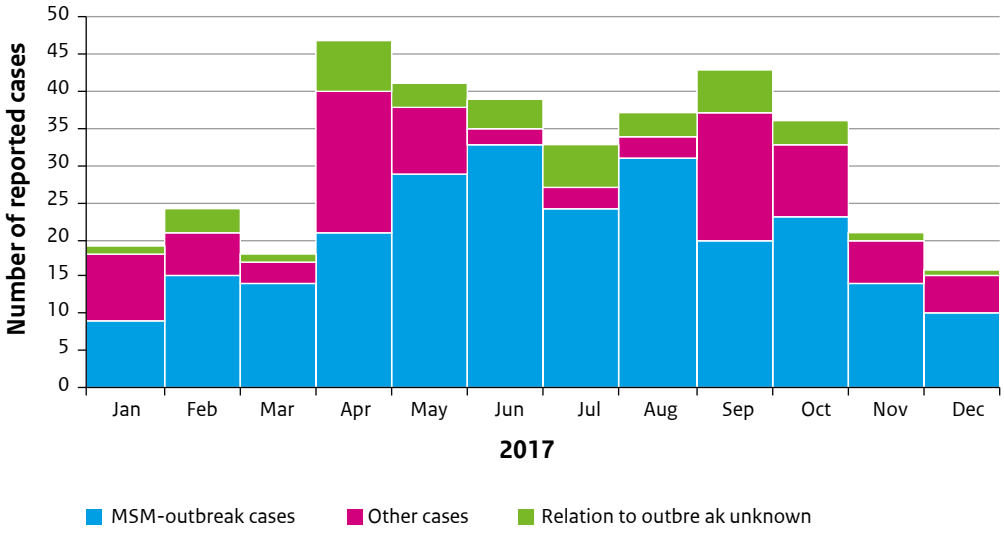

Figure 9.1.3 Distribution of reported hepatitis A-cases per month, 2017
Source: Osiris and laboratory surveillance data

9.1.3 Epidemiology

In 2017, 374 cases of hepatitis A were reported in the Netherlands, corresponding to 2.2 cases per 100,000 population. This is the highest number of reported cases since 2005 (Figure 9.1.1 / Appendix 2). After several years without cases in MSM, nine cases were registered in the second half of 2016. In 2017, the number of MSM cases increased sharply with 243 outbreak-related cases. These cases are part of an ongoing international outbreak among MSM with three different strains dominating [1]. For every two MSM cases, one person from the general population was infected in 2017 [2]. A comparison of cases related and unrelated to the MSM outbreak revealed that almost none of the outbreak-related cases (2%) had travelled to an endemic country compared to 36% of the unrelated cases. A total of 9 children (4% of the outbreak-related cases) were reported related to the outbreak compared to 32 children (35%) among cases unrelated to the outbreak. Spillover of the infection was more common to non-MSM men (57% of the non-MSM men was related to the outbreak) than to women (32% related to the outbreak). The HIV-status was known for 102 MSM cases, of whom 30 (29%) were HIV-positive. In the first six months of 2018, the MSM outbreak is fading out (37 cases), but is not over yet. In 2017, 92 cases were unrelated to this outbreak, which is comparable to the number of reported cases in the period 2011 -2016, i.e. 80–124 cases yearly. Thirty-nine cases could not be assigned, as no strain information was available and they had no direct epidemiological link to a case with available strain information.

No mortality due to hepatitis A was reported in 2017. The age distribution in the period 2008-2017 is given in Figure 9.3.2. The increase in cases in 2017 was mainly in adults, especially those aged 20-49. In total, 90 patients were hospitalised (24%), which is an increase in absolute numbers, but the proportion is comparable to previous years (2010-2016: 20-29%).

The percentage of travel-related cases was 40% -59% in previous years (2008-2016), except in 2010 (31%). In 2017, the proportion of travel-related cases was low with 28% (Figure 9.1.1). Most outbreak-related cases were infected in the Netherlands, and rarely in endemic countries. Among travel-related cases, Morocco (22/103; 21%) was reported most frequently, all by cases not related to the MSM outbreak; Spain was mentioned by 20 cases (19%) of whom 19 were related to the MSM-outbreak.

9.1.4 Pathogen

Hepatitis A virus (HAV) specific IgM-positive samples can be sent to the RIVM-IDS for typing as part of the molecular surveillance of this virus. In 2017, 323 samples of 374 reported cases (86%) were submitted for virus typing. Samples from the remaining 51 cases were not submitted for various reasons; in some cases because the Municipal Health Service had already identified the source. In these cases, it is still worthwhile sequencing a sample because the same strain may appear elsewhere, where no clear source is indicated.

Of the sample cases, 317 (98%) were positive by PCR and could be sequenced. A total of 479 serum and faecal samples of 426 unique persons were tested. HAV RNA was detected in 343 samples (81%) and 331, of reported cases, could be typed, which resulted in 113 unique sequences; a total of 305 cases could be assigned to clusters of two or more cases. Within the

MSM-outbreak, three different circulating strains are reported. The most common strain was VRD_521_2016 (n=126), followed by RIVM-HAV16–090 (n=89), and V16_25801 (n=21). The second largest cluster detected consisted of 14 cases; an outbreak investigation led to frozen raspberries [3].

9.1.5 Research

An international study led by Spain, RIVM and ECDC was performed regarding the MSM outbreak. No differences in case characteristics and exposures were seen between the three strains circulating within the outbreak [4].

9.1.6 International developments

Between January 2012 and December 2014, 32 public health responses were identified in the US following a food handler diagnosed with hepatitis A. In addition to a risk assessment of hepatitis A virus transmission through prepared food, post exposure profylaxe (PEP, for instance hepatitis A vaccine or immunoglobulin) was also recommended. Morey et al evaluated the costs of these control activities [5]. The mean total cost per response was estimated at $41,468. These high costs were driven by the large number of people given PEP, even in the case of only one infected food handler without further cases. As in the US hepatitis A vaccination is incorporated in the NIP, limiting PEP to only fellow food handlers could be considered, according to the authors.

A review assessing the use of hepatitis A vaccine in adults aged over 40, especially as postexposure profylaxis, was performed [6]. As the immunogenicity of the vaccine may be diminished in older adults and seroconversion takes longer, it should be administered as soon as possible within 14 days after exposure. The advantages of vaccination compared to immunoglobulin is the better availabilty of the vaccine and benefits from the long term protection.

Two types of hepatitis A vaccines have been used in the Chinese immunisation programme since 2008 [7]. Depending on the geographical region, children receive one dose of live attenuated hepatitis A virus vaccine, or two doses of inactivated hepatitis A virus vaccine. Vaccination coverage of the targeted children in both regions was above 98%. Hepatitis A incidence declined in both regions and in all age groups after initiation of the immunisation programme, with 78% in the areas using the live attenuated virus vaccine and 82% in the areas using the inactivated virus vaccine. The difference was not statistically significant.

Lin et al [8] reviewed hepatitis A virus infection and vaccination in HIV-positive patients. Seroconversion rates after 2 doses of vaccination are lower among HIV-positive individuals compared to HIV-negative individuals. Factors related to a poor response are low CD4 cell counts, high plasma HIV RNA loads, a coinfection with hepatitis C, and smoking. Administering a third dose appears to be related to a better durability of seroprotection. Vaccination of HIV-positive MSM in Taiwan in 2015 during an outbreak of hepatitis A among MSM with one of the strains also seen in the international MSM outbreak (RIVM-HAV16–090) showed conversion rates of 41% after the first dose [9]. With the second dose after 6 months, the

seroconversion rates increased to 64% (weeks 28-36 after first dose) in the intention-to-treat analysis, and 94% (weeks 28-36) in the per-protocol analysis.

9.1.7 Literature

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* RIVM publication

9.2 Respiratory Syncytial Virus

D. Reukers, A.C. Teirlinck, A. Meijer, W. van der Hoek, A. Suijkerbuijk, P.B. van Kasteren, W. Luytjes, N.A.T. van der Maas

9.2.1 Key points

- Worldwide, RSV infection causes high morbidity and mortality in infants and the elderly.
- In the Netherlands, RSV mainly causes hospitalisation in infants but is also estimated to cause considerable mortality in the elderly.
- A total of 75 RS-viruses (6%) were detected in 1236 combined nose swabs and throat swabs of ILI and other ARI patients, collected by sentinel GPs in the 2017/2018 respiratory season, compared with 12% in the season 2016/2017 and 5.0%-8.6% in the seasons 2012/2013 - 2015/2016.
- Currently, 18 vaccine candidates are at least in phase 1 clinical trials, but only one of these has reached phase 3, aiming to protect the newborn through maternal vaccination

9.2.2 Tables and figures

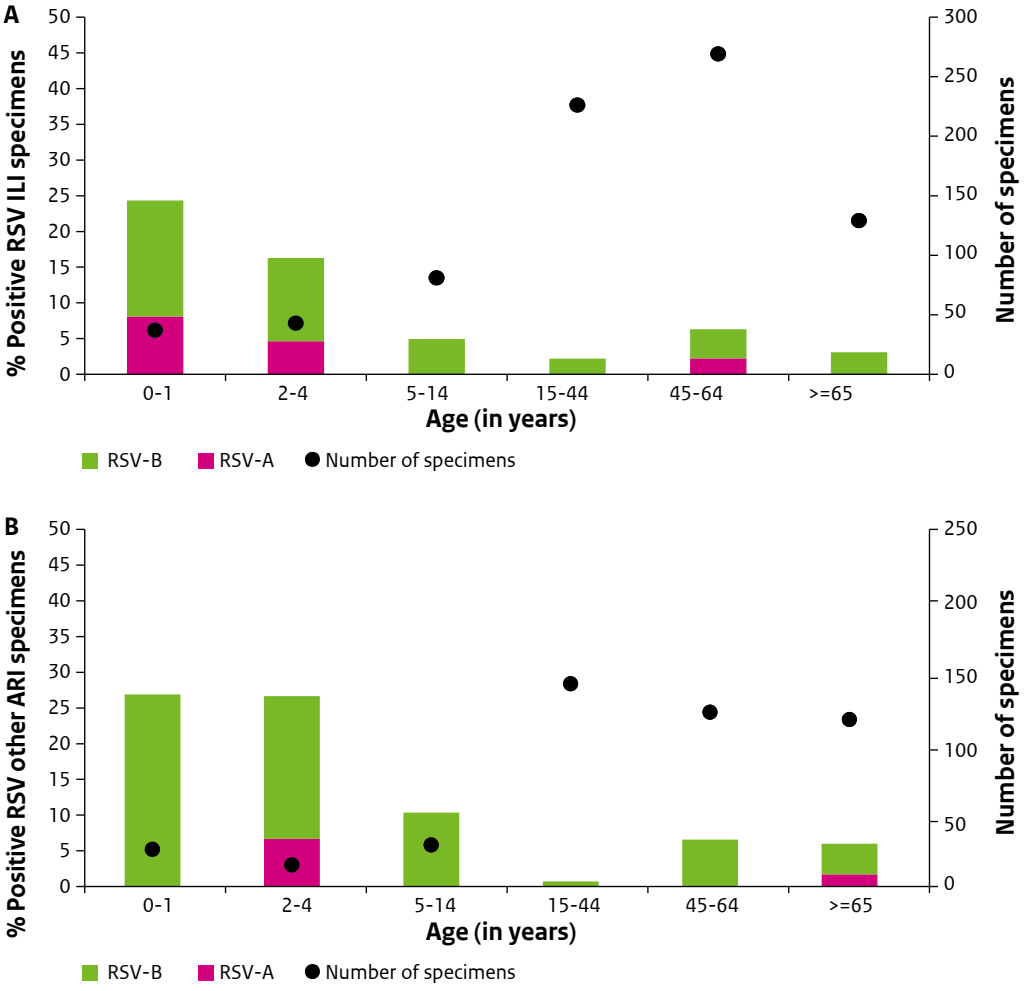

Figure 9.2.1 Percentage of RSV-A and RSV-B positive specimens from patients with influenza-like illness (ILI, panel A) and other acute respiratory infections (ARI, panel B), and the number of tested specimens, taken by sentinel general practitioners (GPs) from community patients during the respiratory season of 2017/2018 (week 40 of 2017 - week 20 of 2018), displayed for six age groups.

Source: NIVEL Primary Care Database, RIVM

Footnote: Please note that for the virological surveillance, the ARI patients do not include the ILI patients.

9.2.3 Epidemiology and pathogen

In the 2017/2018 season, 75 RS-viruses were detected in 1263 nose swabs and throat swabs (6%) collected from patients with ILI or other ARI by sentinel GPs. The percentage of positive specimens from the GP sentinel surveillance was lower in this season compared to 12% in the same period (week 40 2016 until week 20 2017) and comparable to the four seasons before 2016/2017 (range 5.0% - 8.6%).
Of the 76 specimens (one patient had a double infection with RSV-A and RSV-B), 14 were RSV-A (18%) and 62 were RSV-B (82%). The percentage of positive samples was highest in the age group aged below 2 years (24% in ILI cases and 27% in other ARI cases) (Figure 9.2.1).
For more information on epidemiology in the Netherlands, see the annual report 'Surveillance of influenza and other respiratory infections in the Netherlands: winter 2017/2018' [1].

9.2.4 Research

Whereas the majority of RSV vaccines currently in clinical trials aim at the induction of virus-specific antibodies (mainly targeting the F protein), their exact role in protection against infection or severe disease remains unclear. Various strategies are considered for the implementation of RSV vaccines, including immunisation of young naïve infants (<4 months of age), naïve infants (>4 months of age), pregnant women, and the elderly. At the RIVM, we aim to obtain a better understanding of the neonatal immune response and the role of (maternal) virus-specific antibodies in protection against severe RSV-mediated disease. This knowledge will be essential for advising on the implementation of future vaccines in the national immunisation program.
An important aspect of the immune response to RSV is the fact that severe disease can occur even in the presence of virus-specific antibodies. Considering that most vaccines aim at inducing these antibodies, it is extremely important to have a good understanding of their role in RSV-mediated disease. Previously, several groups including our own, have shown that neutralizing antibody concentrations do not correlate with disease severity in infants [2]. In addition, we have shown that RSV-specific antibodies can increase infection of cells belonging to the immune system via a process called antibody-dependent enhancement (ADE) of infection [3]. To follow up on this work, we are currently investigating whether antibody characteristics and effector functions other than neutralization correlate to disease severity on RSV infection. In the past year, we have shown in collaboration with the Radboud UMC Nijmegen that the *in vitro* capacity of RSV-specific antibodies to induce ADE of infection does not correlate with disease severity in a cohort of young infants [4].

9.2.5 International developments

RSV is subdivided in RSV-A and RSV-B, mainly based on the variation in the attachment protein, the G-protein. Currently, no vaccine for RSV is available, but 18 vaccine candidates are at least in phase 1 clinical trials. Most of these vaccine candidates are based on the fusion protein (F-protein) and target different age groups [http://www.path.org/publications/files/CVIA_rsv_snapshot_fsl.pdf.].

Novavax's Prepare *Phase 3 clinical trial* of the RSV F nanoparticle vaccine, in healthy, third-trimester pregnant women in May 2018 reached the milestone of 4,600 participants, of whom at least 3,000 received the RSV F vaccine. An interim report for the trial will be presented in 2019 and, if successful, the vaccine will be put up for market approval in 2020.

MedImmune has a highly potent monoclonal antibody for passive immunisation directed against the F-protein in phase III trial [5, 6].

The World Health Organisation (WHO) started a Global RSV surveillance pilot in 2017, for which case definitions have been established. In the WHO European region, the United Kingdom and the Russian Federation are participating in the pilot. RIVM, together with Statens Serum Institute of Denmark are coordinating efforts to improve RSV surveillance in EU member states, in collaboration with ECDC and under the REspiratory Syncytial virus Consortium in EUrope (RESCEU) project within the framework of the Innovative Medicines Initiative 2 (IMI-2). As part of the RESCEU project, the RIVM has developed a novel RSV pentaplex immuno assay (RSV-MIA). RIVM is also involved in other tasks under the RESCEU project with the aim of developing robust evidence on RSV disease burden and its economic impact in Europe (*http://resc-eu.org/*).

9.2.5.1 Cost effectiveness

The burden of RSV in children aged under 5 in England was assessed [7]. In addition, the cost-effectiveness of different RSV immunisation strategies: targeting vaccination for infants, or pregnant women, or prophylactic antibodies for neonates was evaluated. RSV is responsible for 12 primary care consultations (95% CI 11·9–12·1) and 0·9 admissions to hospital annually per 100 children aged under 5 (95% CI 0·89–0·90), with the major burden occurring in infants younger than 6 months. The most cost-effective strategy was to selectively immunise all children born before the start of the RSV season (maximum price of £220 [95% uncertainty interval (UI) 208–232] per vaccine, for an incremental cost-effectiveness ratio of £20,000 per quality-adjusted life-year).

9.2.6 Literature

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* RIVM publication

9.3 Rotavirus

J.D.M. Verberk, A.W.M. Suijkerbuijk, H. Vennema, M. Hooiveld, H.E. de Melker, P. Bruijning-Verhagen

9.3.1 Key points

- As expected, 2017 showed an average rotavirus epidemic (n=1,047), supporting the hypothesis of a biennial pattern of rotavirus in the Netherlands. However, observations for 2018 up to week 19 show a similar pattern to those seen in years before the low seasons, in contrast to the hypothesis of a biennial pattern.
- G3P[8] was the most prevalent genotype in 2017.
- The Ministry of Health, Welfare and Sport has decided to vaccinate high-risk group children against rotavirus through the NIP.

9.3.2 Tables and figures

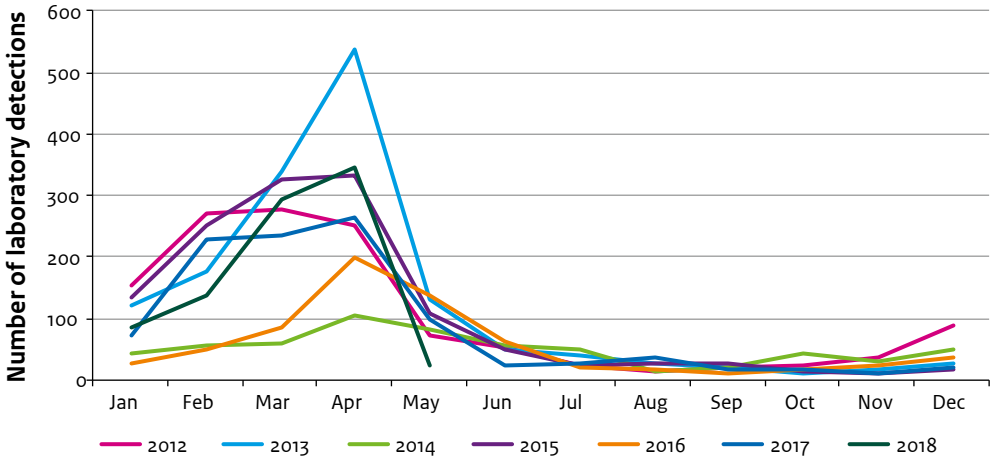

Figure 9.3.1 Reported laboratory detections of rotavirus per month, the Netherlands, 2012-2018

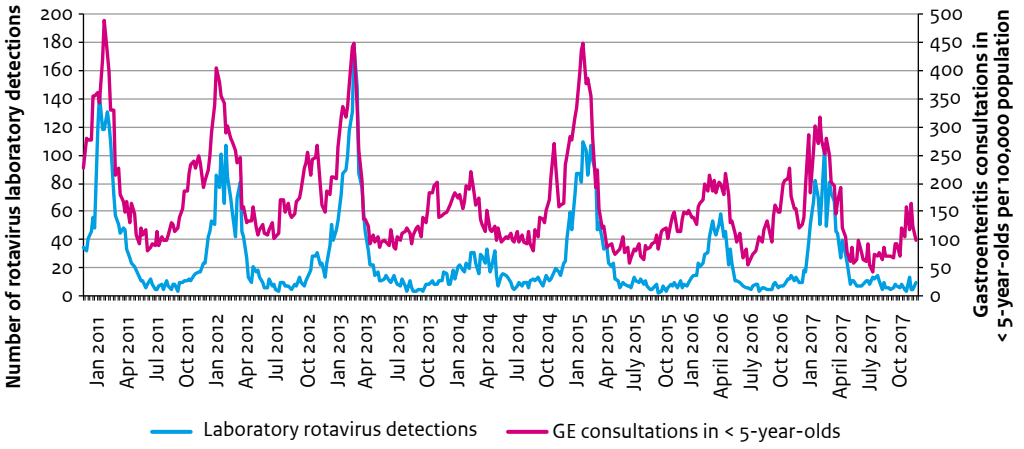

Figure 9.3.2 Rotavirus laboratory detections and general practice gastroenteritis consultation rates in children aged under 5, the Netherlands, 2011-2017

Table 9.3.1 Number of rotavirus samples typed per year, the Netherlands, 2012-2017

Type	2012	2013	2014	2015	2016	2017	Total
G12P8	4	1	6	2	0	1	14
G1P8	48	**83**	20	25	9	23	185
G2P4	23	41	29	34	12	12	139
G3P8	50	51	7	14	23	**38**	145
G4P8	39	35	12	**137**	3	23	226
G9P8	**71**	23	**49**	32	**59**	20	234
Other	36	53	16	28	12	50	195
Total	**271**	**287**	**139**	**272**	**118**	**167**	**1254**

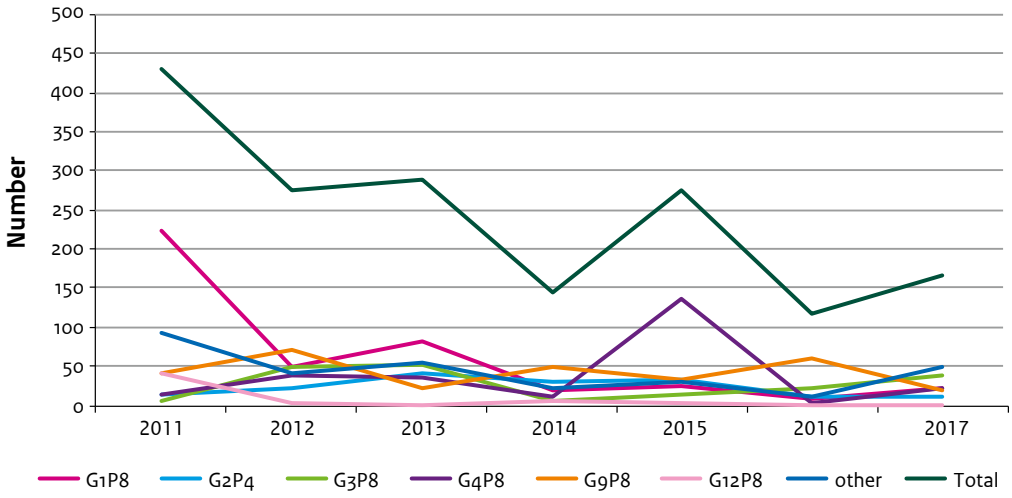

Figure 9.3.3 Distribution of rotavirus genotypes per year, the Netherlands, 2011-2017

9.3.3 Epidemiology

Every week, the Working Group Clinical Virology report laboratory detections which are used for the surveillance of several viral infections, such as rotavirus. These data show an average rotavirus season in 2017 (n=1,047) after two low rotavirus seasons in 2014 and 2016 (2014: N=607, 2016: N=679), and a usual epidemic in 2015 (N=1,323), supporting the hypothesis that in the Netherlands the rotavirus epidemiology is shifting from an annual pattern to biennial epidemics [1]. Based on this hypothesis, 2018 had to be a low season; however data from 2018 till week 19 show an average epidemic, thereby contrasting the hypothesis of a biennial pattern (Figure 9.3.1). Close monitoring for future years is required as the rotavirus epidemiology in the Netherlands has been unstable the last four years.

The Nivel Primary Care Database GP consultations for all-cause gastroenteritis (GE) in children aged under 5 show a mild peak in 2017 (Figure 9.3.2) [2]. The mean weekly all-cause GE consultation rate in the calendar year 2017 was 114 per 100,000 children aged under five (range 32-275 per 100,00 children) compared to 125/100,000 and 135/100,000 in 2016 and 2015, respectively.

9.3.4 Pathogen

The IDS/RIVM received 191 faecal samples to test for rotavirus from laboratories participating in the Working Group Clinical Virology in 2017. Of these, 167 (87.4%) samples could be typed (Table 9.3.1). The most prevalent genotype in 2017 was G3P[8] accounting for just 22.7% of all typed strains; it has not been determined as most dominant before. The most common dominant strains are normally G1P[8] and G9P[8], but in 2017 they declined to 13.7% and 11.9%, respectively (Figure 9.3.3).

9.3.5 Research

In 2017, the RotaFam study was completed. This household study among families with young children assessed the burden and transmission of viral acute gastroenteritis (GE) during two consecutive winter seasons in the Netherlands (2016 and 2017). Among 604 households, ≥1 GE episode occurred in 358 (59%) households (total GE episodes: 708). GE incidence rate was highest for children aged under 2 (IR: 6.2/100 person-weeks during epidemic season). Viruses were detected in 45% of episodes tested (257/565), most commonly norovirus (n=135, 24%), followed by rotavirus (n=76, 13%). Severe GE (Vesikari score (MVS) ≥11) was only observed in children aged under 2 and most common for rotavirus GE (p=0.006). In 52 episodes, a healthcare contact was required (7.3%) but there were no hospitalisations. Secondary GE (occurring within 14 days of a household index case) occurred in 42% after a viral GE index case. This was most frequent after rotavirus (50%) and norovirus (43%) index cases. Further analysis of study results is currently ongoing.

In 2017, all 13 hospitals participating in the project on Risk-Group Infant Vaccination Against Rotavirus (RIVAR) implemented rotavirus vaccination as part of routine care for medical risk infants. Based on a prospective cohort of 466 unvaccinated risk infants who were recruited pre-implementation, we assessed the incidence and disease burden of GE in this population up to 18 months of age. Included infants had either 1.) prematurity, 2.) low birth weight or 3.) a severe congenital condition. The mean GE IR was 74/100 person-years (py) (95%-CI 67-81/100py) and increased with age (46/100py vs. 84/100py per 1-5 months vs. 6-18 months, respectively). Norovirus (24%) and rotavirus (18%) were the dominant pathogens. In total, 142 of 388 (37%) GE episodes required healthcare. Severe GE (MVS ≥11) occurred most frequently in rotavirus positive episodes (59%). The observed GE incidence, severity, and healthcare usage among medical risk infants confirms substantial disease burden and marks these children as a priority group for GE prevention. This cohort will serve as the control group for the evaluation of rotavirus vaccine effectiveness in medical risk infants, the primary objective of the RIVAR project.

9.3.6 Cost-effectiveness

For the Netherlands, the cost-effectiveness analysis published in 2013 [3] has been updated based on more recent data on rotavirus disease burden in the Netherlands and on international evidence of herd-protection in case of universal infant vaccination. The analysis showed that the targeted rotavirus vaccination of infants with medical risk conditions is cost-saving under all tested scenarios, from both the healthcare payer and societal perspective at rotavirus vaccine market prices (€135/child) [4].The cost-effectiveness ratio for universal vaccination was €51,277 at the assumed vaccine price of €75/child, using a societal perspective and 3% discount rates. Universal vaccination became cost-neutral at €32/child. This update was adopted in the recommendations made by the Dutch Health Council published in September 2017 [5]. The Ministry of Health, Welfare and Sport has decided to vaccinate high-risk group children against rotavirus through the NIP.

9.3.7 International developments

As of April 2018, worldwide, 88 countries have introduced rotavirus vaccination in their national immunisation programmes [6]. In addition, 7 countries have either phased or sub-national introductions. Of the ten countries with the highest numbers of rotavirus-related deaths, only six have introduced rotavirus vaccination (Afghanistan, Angola, Ethiopia, India, Kenya, and Pakistan) [6]. Countries in the WHO African region had the greatest proportion of introductions (37%, 31/84) by December
2016 and a great majority of these (77%, 24/31) were supported by new vaccine introduction (NVI) grants from Gavi [7].

In January 2018, Indian vaccine manufacturer Bharat Biotech obtained WHO prequalification of their oral rotavirus vaccine, ROTAVAC [8]. This global certification stating that the vaccine meets all quality, efficacy, and safety standards is a crucial step for global access. The vaccine originated in India from an attenuated (weakened) strain of rotavirus that was isolated from an Indian child at the All India Institute of Medical Sciences in New Delhi in 1985-86 [9]. In India the ROTAVAC vaccine has already been introduced in nine states, in preparation for a national roll-out in the near future [9].

9.3.7.1 Cost-effectiveness

In 2014, rotavirus vaccination with Rotarix was included in the Norwegian national immunisation programme. Before introduction, rotavirus vaccination was expected to be cost-effective from a societal perspective, including productivity losses. Hansen et al. [10] re-evaluated the cost-effectiveness of rotavirus vaccination in Norway using new data on the incidence and economic effects of rotavirus disease. Using a dynamic transmission model, the cost-effectiveness of the ongoing two-dose vaccination programme with Rotarix, and a hypothetical 3-dose programme with RotaTeq was compared with a no vaccination policy. In the base case, and using a healthcare perspective, the incremental cost-effectiveness ratio (ICER) was €47,447 for Rotarix and €52,709 for RotaTeq. Vaccination was cost-saving from the societal perspective. The authors conclude that the childhood rotavirus vaccination in Norway has reduced the rotavirus disease burden substantially, and is cost-effective compared with no vaccination.

9.3.8 Literature

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* RIVM publication

9.4 Varicella zoster virus (VZV) infection

E.A. van Lier, A.W.M. Suijkerbuijk, P.T. de Boer, M. Nielen, W. Luytjes, H.E. de Melker

9.4.1 Key points

- The VZV epidemiology (incidence of GP consultations, and deaths) in the Netherlands has not changed in recent years and is comparable to previous years; in 2016 GPs recorded 240 varicella and 530 herpes zoster episodes per 100,000 population.
- Shingrix®, a subunit vaccine, was registered in 2018 for the prevention of herpes zoster (HZ).
- In a recent cost-effectiveness analysis for the Netherlands, Shingrix® was found to be superior in reducing the burden of HZ compared to Zostavax® alternatives, but the cost-effectiveness depended largely on the vaccine price.

9.4.2 Tables and figures

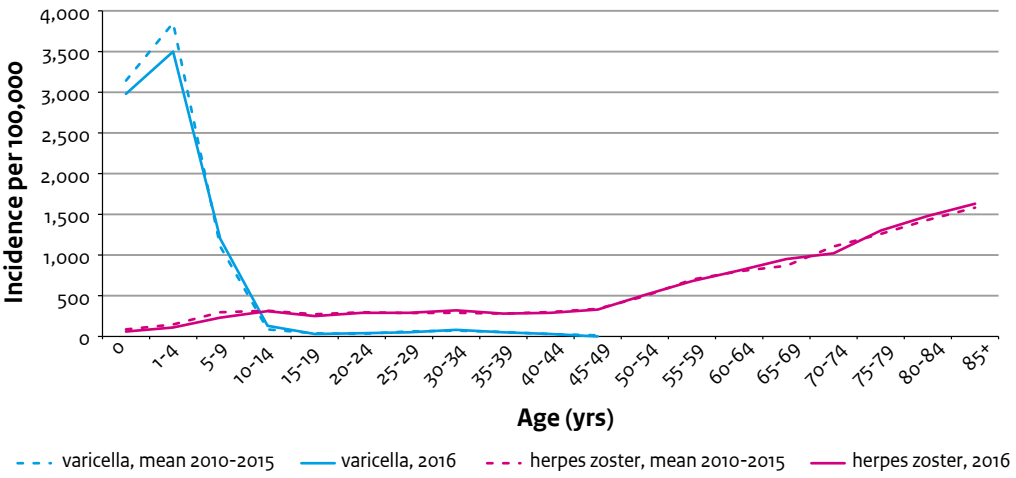

Figure 9.4.1 Estimated incidence per 100,000 population of episodes of varicella (ICPC-code A72) and herpes zoster (ICPC-code S70) in 2016 versus mean 2010-2015 by age group [1]

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

Source: NIVEL

Table 9.4.1 Estimated incidence per 100,000 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 (2010–2016) (rounded off to closest ten)

Syndrome	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Varicella*	190	300	210	(160)	(110)	(180)						
Varicella**	130	260	230	290	180	210	230					
Varicella***						310	270	250	280	270	250	240
Herpes zoster**	350	370	310	340	360	360	360					
Herpes zoster***						480	490	510	510	530	530	530

* Dutch Sentinel General Practice Network (CMR) [2]; since 2008, this network has changed from paper registration to electronic reporting, which may have resulted in under-reporting the weekly number of varicella patients. We therefore used data from NIVEL-PCD from 2008 onwards.
** NIVEL-PCD, old method [3].
*** NIVEL-PCD, new method from 2012 onwards [1]; 2010–2012 recalculated.
Source: NIVEL

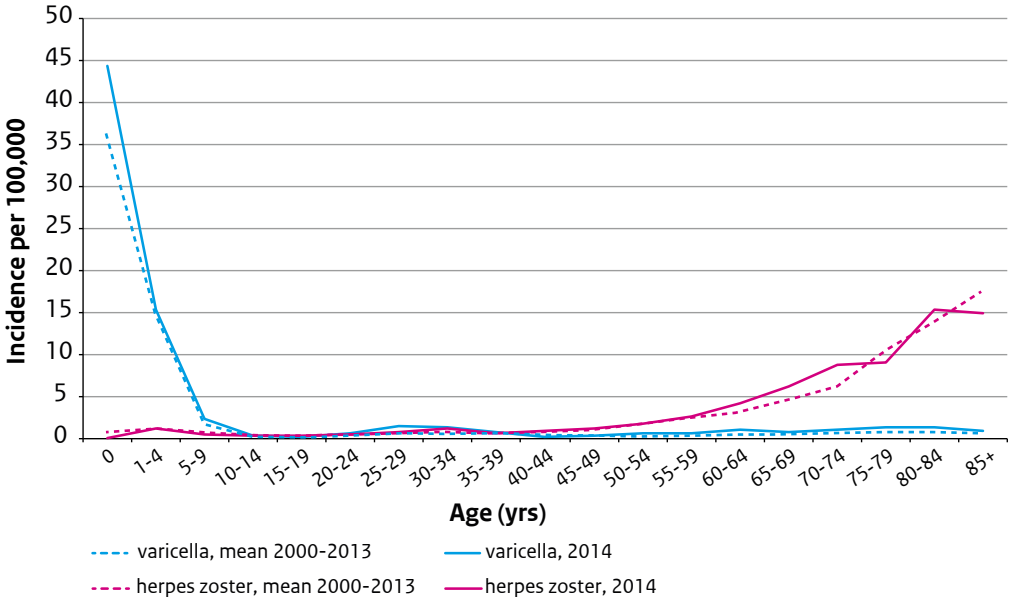

Figure 9.4.2 Incidence per 100,000 population of hospitalisations due to main diagnosis of varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02) in 2014 versus mean incidence in 2000–2013 by age group [4]
Note: hospitalisation data since 2015 is not yet available.
Source: DHD

Table 9.4.2 Incidence per 100,000 population of hospitalisations due to main diagnosis of varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02), 2005–2014 [4]

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

Notes:
In 2006/2007 a number of hospitals stopped their registration, causing an underestimation of hospital admissions from 2006 onwards (see Appendix 1).
Admissions for one day have been excluded.
The number of admissions can be higher than the number of hospitalised patients reported here because some patients are admitted more than once within the same year.
Hospitalisation data since 2015 is not yet available.
Source: DHD

Table 9.4.3 Absolute number of deaths with primary cause of death varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02), 2005–2017 [5]

Syndrome	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017*
Varicella	1	3	5	0	1	2	1	2	1	2	2	4	3
Herpes zoster	15	24	21	14	20	25	20	21	21	26	33	27	33

* Preliminary data
Source: CBS

Table 9.4.4 Vaccine effectiveness of Zostavax®

Study setting, period [reference]	Population	Follow-up period	Adjusted vaccine effectiveness (%) HZ incidence	PHN incidence
England, Royal College of General Practitioners, 2005–2016 [6]	70–71 years (routine cohort) 78–80 years (catch-up cohort)	First 3 years First 3 years	62 (50–71) 62 (48–72)	88 (59–100) 70 (39–93)
United States, Kaiser Permanente Northern California, 2007–2014 [7]	All 50+ years 50–59 years 60–69 years 70–79 years 80+ years 50–59 years 60–69 years 70–79 years 80+ years	Whole follow-up period First 3 years First 5 years 	49.1 (47.5–50.6) 59.5 (51.7–66.1) 54.7 (52.3–57.0) 49.8 (46.6–52.8) 48.0 (42.5–53.0) - 49.2 (46.8–51.5) 45.5 (42.5–48.4) 43.9 (38.3–49.0)	
United Kingdom, primary health care records, 2013–2016 [8]	70–71 years (routine cohort) plus 79 years (catch-up)	First 3 years	64 (60–68)	81 (61–91)
Canada, Alberta Health Care Insurance Plan Registry [9]	All 50+ years	First year Fifth year	50.0 (44.7–54.8) 14.0 (-21.0–38.9)	

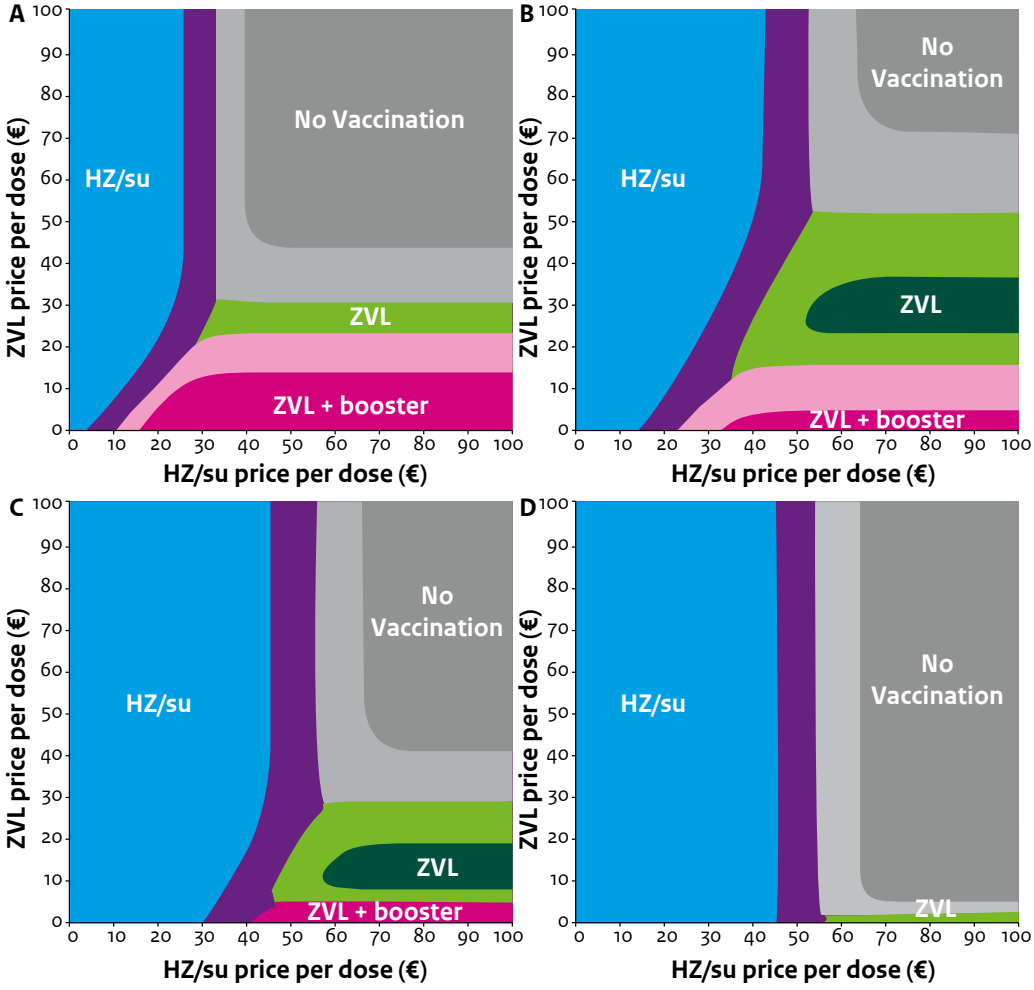

Figure 9.4.3 Two-way sensitivity analysis of the vaccine price per dose of Shingrix® and Zostavax® of (A) 50-year-olds, (B) 60-year-olds, (C) 70-year-olds, and (D) 80-year-olds. After performing a probabilistic sensitivity analysis using 10,000 Monte Carlo simulations, the alternative with the highest probability of being cost-effective to a willingness-to-pay threshold of €20,000 per QALY gained is presented over a range of vaccine prices. Light coloured areas indicate that the alternative had the majority of simulations with highest net-monetary benefit, while dark coloured areas indicate that the proportion of simulations was ≥90%. HZ/su: Shingrix®, ZVL: Zostavax®.

9.4.3 Epidemiology

The VZV epidemiology in the Netherlands is comparable to previous years (Table 9.4.1 and Table 9.4.3). Unfortunately, there is no update on hospitalisations for the years 2015–2017 (Table 9.4.2). The incidence of varicella episodes per 100,000 population is highest in the children aged under five, whereas the incidence of herpes zoster (HZ) episodes is highest in those aged over 50 (Figure 9.4.1). According to a new, more precise method for estimating morbidity rates used by NIVEL from 2012 onwards, the incidence of HZ is higher than it was according to the old method (Table 9.4.1) [1, 10]. The incidence of hospitalisations due to varicella is highest among newborns, while the incidence of hospitalisations due to HZ is highest among the oldest age groups (Figure 9.4.2). Mahamud et al. found that national death certificate data tend to overestimate the number of deaths in which HZ is the underlying or contributing cause of death [11]. If we apply their rate of deaths for which HZ was validated as the underlying cause of death (0.25 (range 0.10–0.38) per 1 million population) to the Dutch population in 2017, we would expect 4.3 deaths (range 1.7–6.5) instead of the 33 deaths reported in 2017 (Table 9.4.3).

9.4.4 Research

Recent research conducted in the Netherlands among asylum seekers aged 18-45 years shows that the protection against varicella among the investigated groups (Syria, Iran, Iraq, Afghanistan and Eritrea) is also high: 96% (range 92-98%) [12]. However, research among asylum seekers in Germany, Canada and Italy showed that seroprevalence differs considerably between countries of origin, and depends on the age of the person concerned [13-15].

A recent Dutch study showed that pre-vaccination VZV specific T-cell immune responses affect vaccine induced immune responses by Zostavax® in people aged 50-65 [16]. Long-term enhancement of VZV specific T-cell responses upon VZV vaccination was induced only in persons with low pre-vaccination T-cell immunity.

In a recent cost-effectiveness analysis for the Netherlands, de Boer et al. investigated the cost-effectiveness of different vaccination strategies compared to no vaccination:
1. Two doses of Shingrix® within 2-6 months
2. One dose of Zostavax®
3. One dose of Zostavax® with a booster after 10 years.

Shingrix® was found to be superior in reducing the burden of HZ compared to both Zostavax® alternatives, but the cost-effectiveness depended largely on the vaccine price. A two-way sensitivity analysis showed that there were vaccine price combinations of Shingrix® and Zostavax® in which either Shingrix® (two doses), Zostavax® (one dose) or Zostavax® (one dose plus booster after 10 years) could be the most cost-effective alternative (Figure 9.4.3).
The optimum vaccination age of Shingrix® was 60–80 years with a corresponding maximum vaccine price of €52.15– €54.54 per dose to remain cost-effective (defined as less than €20,000 per QALY gained). The maximum vaccine price of Zostavax® varied considerably by age, ranging from €51.40 per dose for 60-year-olds to €0.73 per dose for 80-year-olds [17]. In this study, the incremental cost-effectiveness ratio (ICER) of Zostavax® was higher than in previous

analyses for the Netherlands [18, 219], mainly due to a lower QALY loss per HZ case, the exclusion of additional protection against PHN and HZ-related burden of illness, and inclusion of updated incidence rates and long-term follow-up data of Zostavax® efficacy.

9.4.5 International developments

9.4.5.1 Varicella

Zhu et al. conducted a meta-analysis on the incidence rate of breakthrough varicella after 1 or 2 doses of varicella vaccine. The pooled 1-dose and 2-dose average breakthrough incidence rates were 8.5 (95%CI: 5.3–13.7) and 2.2 cases per 1,000 person-years (95%CI: 0.5-9.3), respectively for varicella episodes with any number of lesions in healthy children. They concluded that two doses of varicella vaccine are more effective than one, and 3–4 years between the first and second vaccinations may achieve higher efficacy [20].
Yin et al. conducted a meta-analysis on the effectiveness, immunogenicity and safety of one-dose versus two-dose varicella vaccination. The incremental efficacy of two-dose vaccination was 79% (95%CI: 56–90%) in randomised controlled trials, 63% (95%CI: 36–79%) in cohort studies, and 81% (65–90%) in case-control studies. They concluded that two-dose varicella vaccination resulted in higher levels of immunogenicity and provided superior protection compared to one-dose vaccination [21].
Henry et al. studied the long-term efficacy of varicella vaccination up to six years post-vaccination. Efficacy of two doses of MMRV against all and against moderate or severe varicella was 95.0% (95%CI: 93.6–96.2%) and 99.0% (95%CI: 97.7–99.6%), respectively. Efficacy of one dose of varicella vaccine against all and against moderate or severe varicella was 67.0% (95%CI: 61.8–71.4%) and 90.3% (95%CI: 86.9–92.8%), respectively [22].
In Germany, varicella vaccination rates differed between regions and were lower than for measles. Although vaccination rates have increased, they are insufficient to prevent outbreaks. Recommendation by the physician had the strongest impact on varicella vaccination [23].

9.4.5.2 Herpes zoster

In 2018, HZ/su or Shingrix® was registered for the prevention of HZ among immunocompetent people aged 50 and older. The vaccine was developed to be given in a two-dose schedule, with the second dose given 2-6 months after the first. Because of the recent registration of this new vaccine, the Health Council of the Netherlands will reconsider the vaccination recommendations against HZ.

Recently, the Advisory Committee on Immunisation Practices (ACIP) recommended that Shingrix® is preferred to Zostavax® for the prevention of HZ and related complications, that the target group be extended to all immunocompetent ≥50-year-olds, and that individuals previously vaccinated with Zostavax® should be revaccinated [24].
Serological research showed that immune responses of Shingrix® persisted for 9 years, and no vaccine-related serious adverse events or suspected HZ breakthrough episodes were reported. Based on modelling using existing data, immune responses are predicted to remain above pre-vaccination levels after 15 years [25].

The safety profile of Zostavax® after 10 years of post-marketing use (>34 million doses distributed worldwide) remain favourable and consistent with observations in clinical trials and earlier post-licensure studies; the majority (93%) of reported adverse events were non-serious, and local injection site reactions were reported most frequently [26]. Table 9.4.4 presents an overview of recent studies on vaccine effectiveness of Zostavax® conducted in different populations in real-world settings.

9.4.5.3 Cost-effectiveness

In a retrospective study conducted between 2004-2014, costs due to varicella related hospitalisations, primary healthcare visits, and productivity losses were assessed in the population of Aragón (Spain) [27]. In order to conduct a cost-benefit assessment, these total costs were compared to the expenses that would have been incurred due to varicella vaccination, assuming 100% vaccination coverage. A benefit-cost ratio of 1.6 was estimated considering that all children had been vaccinated and received a booster vaccination at a price of €28.59 per dose. A benefit-cost ratio of 1.24 was found if only one vaccination dose for every 1-year-old individual was taken into account. Given that the benefit-cost ratios were estimated above 1, varicella vaccination has the potential to be cost-saving.
Before the recent recommendation on the preferential use of Shingrix®, a single dose of Zostavax® was recommended in the US for all people aged ≥60. As vaccine-induced protection of Zostavax® decreases to zero within 10 years, Le and Rothberg assessed the cost effectiveness of an HZ vaccine booster and its optimal timing from a societal perspective [28]. Using a Markov model, they found that the optimal timing of the booster was after 10 years and that the ICER varied from $32,950 (initial dose administered at 60 years) to $63,591 (initial dose administered at 80 years).
Le and Rothberg also assessed the cost-effectiveness of the new adjuvanted subunit vaccine Shingrix® in the US from a societal perspective [29]. Using the same Markov model and vaccine efficacy data from randomised clinical trials, they found that, at a price of $280 per series ($140 per dose), Shingrix® was more effective and less expensive than Zostavax® at all ages. Compared to no vaccination, the ICERs of vaccination with Shingrix® ranged from $20,038 to $30,084 per QALY, depending on vaccination age. Furthermore, Shingrix® resulted in less overall costs than Zostavax® and had the highest probability of being cost-effective.

9.4.6 Literature

9.4.6.1 References

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10
Vaccines in development for other potential future NIP target diseases

N.Y. Rots

10.1 Vaccines under development

An update of information with regard to vaccines in development for infectious diseases that have reached the clinical testing phase and are relevant for the Netherlands is given in the table below. Vaccine development takes 10-15 years and only a small percentage (6%) of vaccines tested in phase I reach marketing authorisation. On average, clinical development phase I takes 1-2 years, phase II 2-3 years and phase III 4-6 years.
Relevant developments of combination vaccines have been described in earlier chapters. Compared with the last reporting year a Herpes Zoster vaccine (Shingrix) has been licensed and is already being used in several countries. A lyme vaccine received a fast track designation by the FDA based on positive results of the phase I trial. New safety data of the first licensed Dengue vaccine (Dengvaxia) indicating an increased risk of hospitalised and severe dengue in seronegative individuals have been reported. The Strategic Advisory Group of Experts (SAGE) recommends a "pre-vaccination screening strategy" followed by vaccination of only dengue-seropositive persons. An Ebola vaccine candidate is being used in outbreak settings. Less funding is available for Zika vaccine development, putting the start of a phase III trial on hold.

10.2 Tables and figures

Pathogen	Vaccine	Status, clinical phase
Bacteria		
Chlamydia	Adjuvanted chlamydia vaccine CTH522 (SSI)	I
Clostridium difficile	Toxoid inactivated	III, FDA fast track (Sanofi Pasteur) program ended
	Recombinant toxoid	III fast track (Pfizer)
	VLA84, genetic fusion (Valneva)	II completed, phase III waiting for partner
Helicobacter pylori	HP3 (Chiron/Novartis)	I, completed, limited protective immunity, not pursued
	Oral recombinant vaccine (China)	III, discontinued
Lyme	Outer surface protein based vaccine (GSK)	Licensed but removed from market in 2002 due to poor market performance
	Subunit vaccine VLA15 (Valneva)	I, II end 2018 (fast track FDA)

Pathogen	Vaccine	Status, clinical phase
Meningococcal ABCWY	MenACWY combined with Men B	II adolescents
	Novartis/GSK, Pfizer	I
Moraxella catarrhalis, non-typeable *Haemophilus influenzae*	Recombinant, COPD reduction (GSK)	II
Shigella	Live attenuated single-strain	II
	Inactivated trivalent whole cell	I
	Chemical glycoconjugate	III
	recombinant glycoconjugate (biconjugate)	III
	conjugate outer membrane (Novartis/GSK)	II
Staphylococcus aureus	Conjugate (SA4Ag, 4 antigen), fast track FDA (Pfizer)	II Previous phase I-III with different single antigen vaccine candidates all failed, safety concerns and low efficacy
	Protein	I
Streptococcus group A & B	-Group A: N-terminal M protein-based multivalent vaccines (26-valent and 30-valent vaccines)	II
	Conserved M protein vaccines (the J8 vaccine and the StreptInCor vaccine)	I
	-Group B: CPS-protein conjugate (mono and trivalent) (GSK)	II maternal
	6-valent polysaccharide CRM197 conjugated vaccine (Pfizer)	I maternal

Pathogen	Vaccine	Status, clinical phase
Tuberculosis (all forms all ages)	Live attenuated vaccine BCG	On market but low efficacy
	• 2, 3 or 4 antigen adjuvanted fusion protein (GSK/Areas, Areas)	II(b)
	• subunit adj recombinant fusion protein (Areas/Sanofi/SSI)	II completed
	• Modified recombinant BCG	II
	• recombinant subunit (GSK, Sanofi)	II
	• Live attenuated (MTBVAC)	IIb start 2018
	• Lysate of NTM	III
	• killed whole cell (booster) (Areas)	I
	• viral vector (Oxford)	I
Viruses		
Chikungunya	Live recombinant Measles Virus based Virus-like particle (NIAID)	II Immunogenic and safe in adults
Cytomegalo (CMV)	Glycoprotein B	I and III
	DNA (Astellas/ Vical) eVLP	III
	replication defective V160 (MSD)	II
	Stemcell transplant patients (Merck)	Approved US 2017
Dengue	Live recombinant (tetravalent)	III
	(Butantan/NIAID)	III
	Live-attenuated (tetravalent) TDV (Takeda)	I
	Inactivated (tetravalent) V180(Merck)	II
	Recombinant subunit (tetravalent) (GSK) Monovalent subunit DNA	Dengvaxia Sanofi registration approved for people aged 9-45

Pathogen	Vaccine	Status, clinical phase
Ebola	rVSVΔG-ZEBOV-GP V920 (Merck/ NewLink Genetics)	III, used in outbreak Congo
	CAd3-EBOZ (GSK/NIH/NIAID)	III ready to start
	Ad26-EBOV and MVA-EBOV (Johnson & Johnson/Janssen vaccines and Bavarian Nordic)	III
	Recombinant nanoparticle based (Novavax)	I
	Recombinant viral vector (GSK)	III, II
	VRC-EBOADC069-00-VP (Okairos, NIAID)	I
Epstein–Barr	Recombinant gp350 Glycoprotein subunit	II
Hepatitis C	Recombinant viral vector (GSK)	II
Hepatitis E	Recombinant protein	II (Hecolin®, Xiamen China Approved in China not registered in EU)
Herpes simplex	HSV-2 replication defective (Sanofi)	I
Herpes zoster (Shingles)	Recombinant (Shingrix, GSK)	Approved US 2018, submitted EU
	Inactivated V212 (Merck)	III, on hold
HIV	Recombinant protein (GSK)	II
	Viral vector Prime/boost (Sanofi)	II
	Ad26 Mos HIV vaccine (Janssen vaccines)	II
	DNA (GeoVax)	II completed
Hookworm	iBio	I
Noro	Virus-like particles (bi-valent) (Takeda)	II
	Oral tablet vaccine (Vaxart)	I
MERS-CoV	MVA-MERS-S DNA (GeneOne Life Science/ Inovio)	I, promising results

Pathogen	Vaccine	Status, clinical phase
Parainfluenza type I	Live attenuated	I-II
Respiratory syncytial (RSV) (17 in clinical development)	Live attenuated (Sanofi/NIH)	I (paediatric)
	Inactivated whole cell	0
	Nanoparticle based (Novavax)	III (maternal data 2021), II (elderly, failed), I infants
	Subunit, F-protein (GSK)	I maternal
	Subunit, F-protein (NIH/NIAID/ VRC)	I (maternal, elderly)
	Subunit, F-protein (Pfizer)	I/II elderly, maternal
	Subunit, F-protein (Janssen)	I (elderly)
	Gene-based vector MVA (Bavarian Nordic)	II (elderly)
	Gene-based vector AV (Janssen)	II (elderly, paediatric)
	Gene-based vector AV (Vaxart)	I (elderly)
	Gene-based vector AV (GSK)	II (paediatric)
Thyfoid	TT-Conjugate (Bharat Biotech)	III
West Nile	Inactivated (NIAID)	I, completed
	Live attenuated Recombinant subunit (NIAID Hawai Biotech)	I, completed
Zika	DNA (GeneOne Life Scinence/ Inovio, NIAID) RNA	II
	Whole inactivated (Sanofi, Takeda, NIAID)	II (Sanofi did not start phase III limited funding Barda)

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

List of abbreviations

4CMenB	multicomponent meningococcal B vaccine
9vHPV	nonavalent HPV-vaccine
AAPC	average annual percent changes
ACIP	Advisory Committee on Immunisation Practices
ADEM	acute disseminated encephalomyelitis
AE	adverse events
AEFI	adverse events following immunisation
AFP	acute flaccid paralysis
AGW	anogenital warts
AIS	adenocarcinoma in situ
AOM	acute otitis media
aP	acellular pertussis
ARI	acute respiratory infections
AS	adjuvant system
ASCUS	atypical squamous cell of undetermined significance and worse
BCG	Bacillus Calmette-Guérin
BES	Bonaire, Sint Eustatius and Saba, the Dutch Caribbean
BMGF	Bill & Melinda Gates Foundation
bOPV	bivalent oral polio vaccine
CAPiTA	Community-Acquired Pneumonia immunization Trial in Adults
CBO	Dutch Institute for Healthcare Improvement
CBS	Statistics Netherlands
CC	clonal complex
CDC	Centres for Disease Control and Prevention
CFR	case fatality rate
CFS	chronic fatigue syndrome
CI	confidence interval
CIb	Centre for Infectious Disease Control
CIN	cervical intraepithelial neoplasia
CMR	Dutch Sentinel General Practice Network
CMV	Cytomegalovirus
COPD	chronic obstructive pulmonary disease
CrI	credible interval
CRM	CRM conjugate
CRPS	complex regional pain syndrome
CSF	cerebrospinal fluid
CSI	Chlamydia trachomatis Screening and Implementation study
CSW	commercial sex workers
CVP	child vaccine provider
DALY	Disability Adjusted Life Years
DAT	Diphtheria antitoxin
DHD	Dutch Hospital data
DNA	desoxyribonucleic acid
DTaP	combination of diphtheria, tetanus and acellular pertussis vaccines
DTaP5	hexavalent diphtheria, tetanus and acellular pertussis vaccine

DTaP-IPC-HepB-PRP-T	hexavalent diphtheria-tetanus-acellular pertussis-inactivated poliovirus-hepatitis B-*haemophilus influenzae* type b vaccine
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
ECDC	European Centre for Disease Control and Prevention
ELS	extensive limb swelling
EMA	European Medicines Agency
EPIS	the Epidemic Intelligence Information System
EU/EEA	European Union / European Economic Area
EV	enterovirus
F	fusion
FDA	Food and Drug Administration
FHA	filamentous haemagglutinin
FIGO 1A	cervical cancer stage 1A
Fim2	serotype 2 fimbriae
Fim3	serotype 3 fimbriae
GAPIII	the WHO global action plan to minimise poliovirus facility-associated risk
GBD	Global Burden of Disease
GBS	Guillain-Barre syndrome
GE	gastroenteritis
GGD	Municipal Health Service
GMC	geometric mean concentrations
GMT	geometric mean titres
GP	General Practitioner
GPLN	WHO Global Polio Laboratory Network
GSK	Glaxo Smith Kline
GUM	genitourinary medicine
GW	genital warts
HAV	hepatitis A virus
HAVANA	Study of HPV prevalence among young girls
HBeAg	hepatitis B viral protein
HBGA	human histo-blood group antigens
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HC	Health Council
HCW	health care workers
HepB	hepatitis B virus
Hib	*Haemophilus influenzae* type b
Hie	*Haemophilus influenzae* type e
Hif	*Haemophilus influenzae* type f

HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HN	haemagglutinin-neuraminidase
HPV	human papillomavirus
HPV2D	Study to monitor the immunogenicity of a two-dose schedule of HPV vaccination
hrHPV	high-risk human papillomavirus
HR	hazard ratio
HSIL	high-grade squamous intraepithelial lesion
HSV	herpes simplex virus
HZ	herpes zoster
IBD	invasive bacterial disease
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
IDU	injecting drug use
IFN-γ	interferon γ
IgG	immunoglobulin G
ILI	influenza-like illness
IMD	invasive meningococcal disease
IMI	Innovative Medicines Initiative
IPCI	Integrated Primary Care Information
IPD	invasive pneumococcal disease
IPV	inactivated polio vaccine
IR	incidence rate
IRR	incidence rate ratio
ITP	idiopathic thrombocytopenic purpura
IU/ml	international units per millilitre
JCVI	Joint Committee on Vaccination and Immunisation
JIM	Juveniele Immunisatie Meningokokken ACWY
JNK	c-Jun N-terminal kinase
LBZ	National Register Hospital care
LINH	the Netherlands Information Network of General Practice
LMR	National Medical Registration
lrHPV	low-risk human papillomavirus
LVC	low vaccination coverage
LYs	life years
LYS	life years saved
MATS	the meningococcal antigen typing system
MCC	meningococcal C conjugate
MCPI	maximum cost-effective price increase
MCV	measles-containing vaccine
ME	myalgic encephalomyelitis
MenACWY-D	quadrivalent meningococcal diphtheria toxoid conjugate vaccine

MenACWY-TT	tetravalent meningococcal tetanus toxoid conjugate vaccine
MenB	Meningococcal serogroup B
MenC	Meningococcal serogroup C
MenC-PS	Meningococcal serogroup C polysaccharide vaccine
MenC-TT	Meningococcal serogroup C polysaccharide-tetanus toxoid
MenW	Meningococcal serogroup W
MenX	Meningococcal serogroup X
MenY	Meningococcal serogroup Y
MERS-CoV	Middle East Respiratory Syndrome-coronavirus
MF	multiplication factor
MIA	multiplexed immuno assays based on Luminex technology
MLST	Multilocus sequence typing
MLVA	multiple locus variable number of tandem repeat analysis
MMR	combination of measles, mumps and rubella vaccines
MMRV	combination of measles, mumps, rubella and Varicella vaccines
MS	multiple scleroses
MST	minimum spanning tree
MSM	men who have sex with men
MuV	mumps virus
NIAID	National Institute of Allergy and Infectious Diseases
NIP	national immunisation programme
NIVEL	Netherlands Institute for Health Services Research
NIVEL-PCD	NIVEL Primary Care Database
NK	Natural killer
NKR	the Netherlands Cancer Registry
NPG	National Influenza Prevention Programme
NPL	National Polio Laboratory
NRBM	Netherlands Reference laboratory for Bacterial Meningitis
NTHi	nontypeable *Haemophilus influenzae* strains
NTM	neurotrimin
NVI	Netherlands Vaccine Institute
OPV	oral polio vaccine
OR	odds ratio
PASSYON	Papillomavirus Surveillance among STI clinic Youngsters
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PCV1	porcine circovirus type 1
PCV7	heptavalent pneumococcal conjugate vaccine
PCV10	10-valent pneumococcal conjugate vaccine
PCV10-7	additional types in PCV10 compared to PCV7
PCV13	13-valent pneumococcal conjugate vaccine
PCV13-10	additional types in PCV13 compared to PCV10
PEF	poliovirus essential facility
PEP	post-exposure prophylaxis
PHiD-CV	10-valent pneumococcal nontypeable Haemophilus influenza protein D conjugate vaccine

PIENTER	assessing immunisation effect to evaluate the NIP
POTS	postural orthostatic tachycardia syndrome
PPV	proportion of population vaccinated
PPV23	23-valent pneumococcal polysaccharide vaccine
PPV23-PCV13	additional types in PCV13 compared to PPV23
PPSV23	23-valent pneumococcal polysaccharide vaccine
Prn	pertactin
PRP	polyribosyl-ribitol-phosphate
Ptx	pertussis toxin
PWP-TT	Prentice Williams and Peterson total time
PY	person years
QALY	quality-adjusted life year
qPCR	real-time polymerase chain reaction
RIVM	National Institute for Public Health and the Environment, the Netherlands
RNA	ribonucleic acid
RR	relative risk
rSBA	rabbit serum bactericidal activity
RSV	respiratory syncytial virus
RT-PCR	reverse transcription polymerase chain reaction
RV	rotavirus
SARIMA	seasonal autoregressive integrated moving average
SAGE	Strategic Advisory Group of Experts
SBA	serum bactericidal antibody
SCCS	self-controlled case series
SHC	sexual health centres
SLE	systemic lupus erythematosus
SLSJ	the Saguenay-Lac-Saint-Jean region in Quebec, Canada
SNP	single nucleotide polymorphism
SpIDnet	The Streptococcus pneumoniae Invasive Disease network
SPR	RIVM strategic programme
STI	sexually transmitted infections
Tdap	tetanus, diphtheria and pertussis vaccine
TIG	tetanus immunoglobulins
TIM	second immunisation Meningococcal serogroup C study
TM	transverse myelitis
tOPV	trivalent oral polio vaccine
TT	tetanus toxoid
UA	under-ascertainment
UE	underestimation
UK	United Kingdom
UR	under-reporting
US	United States
VDPV	vaccine-derived poliovirus
VE	vaccine effectiveness
VLP	virus-like particle

VPD	vaccine-preventable disease
VZV	varicella zoster virus
VWS	Ministry of Health, Welfare and Sport
WGS	whole genome sequencing
WHO	World Health Organization
wP	whole-cell pertussis
WPV	wild poliovirus
WTP	willingness-to-pay
YLD	years lived with disability
YLL	years of life lost

Appendix

Appendix 1 Surveillance methodology

A1.1 Disease surveillance

The impact of the National Immunisation Programme (NIP) can be monitored through mortality, morbidity and laboratory data related to the target diseases. We describe the different data sources used for disease surveillance, and the different methods used to estimate vaccine impact, vaccine effectiveness, burden of disease, and cost-effectiveness.

A1.1.1 Data sources

A1.1.1.1 Notification data

Notifications by law are an important surveillance source for the diseases included in the NIP. The notification of infectious diseases started in the Netherlands in 1865. Since then, several changes in notification procedure have been enforced. Not all diseases targeted by the NIP have been notifiable during the entire period (Table A1.1) [1]. In December 2008, a new law (*Wet Publieke Gezondheid*) was passed that required the notification of all NIP-targeted diseases, except human papillomavirus (HPV)). There are four categories of notifiable disease. Diseases in category A have to be reported directly by telephone following a suspected case. 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 a delay in reporting [2]. In each of the first three categories (A, B1 and B2), different intervention measures can be enforced by law to prevent the spread of the disease.

Physicians and clinical laboratories should notify cases to the Municipal Health Centres (GGDs). The GGDs notify cases to the RIVM through the online platform OSIRIS. In addition to patient characteristics (e.g. year of birth, sex, postal code), epidemiological (e.g. related cases, risk factors) and clinical data (e.g. hospital admission, death, vaccination status) are collected through the notifications.

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, 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	C	from December 2008 onwards
Mumps	C	1975–1999, from December 2008 onwards
Measles	B2	1872–1899, from 1975 onwards
Rubella	B2	from 1950 onwards
Invasive meningococcal disease	C	from 1905 onwards

[a] Only for cases born from 2006

A1.1.1.2 Register based data

A1.1.1.2.1 Death statistics

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 a natural death, the physician should report the illness or disease that has led to death (primary cause), any complication directly related to the primary cause that has led to death (secondary cause), as well as additional diseases and specifics present at the moment of death that 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 10 years or so, which has to be taken into account when identifying mortality trends. Since the statistical year 2013, CBS has used the IRIS programme to automatically code the causes of death [3]. One of the advantages of this is that it increases the international comparability of the figures. The change in coding did however cause (once only) considerable shifts in the statistics.

A1.1.1.2.2 Hospital admissions

Until 2010, hospital data was managed by the research institute Prismant in the National Medical Register (LMR); from 2011, Dutch Hospital Data (DHD) managed the LMR. Since 2013, the National Register Hospital Care (LBZ), managed by DHD, has received the discharge diagnoses of all patients 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. Up to 2012, discharge diagnoses were coded according to the ICD-9 coding system, thereafter according to ICD-10. The coverage of this registration was about 99% until mid-2005. Thereafter, coverage fluctuated due to changes in funding (Table A1.2). The data presented in this report relate only to 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 [4] and by Van der Maas et al. for pertussis [5]. Hospitalisation data from 2015 onwards are not yet available as a result of changing procedures.

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

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

*These numbers are an approximation of the exact percentage
Note: hospitalisation data since 2015 is not yet available
Sources: Statistics Netherlands (CBS) up to 2009 and Dutch Hospital Data (DHD) from 2010 onwards

A1.1.1.2.3 Primary care data

The NIVEL (Netherlands Institute for Health Services Research) Primary Care Database (NIVEL-PCD) includes data from routine electronic medical records of general practitioners (GPs). 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 symptoms and diagnoses of consulting patients 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 are made by extrapolating the reporting rates in these practices to the total number of Dutch residents, as obtained from CBS. For example, incidence rates of varicella and herpes zoster have been calculated using these data.

The current Dutch RSV surveillance is primarily based on general practitioner (GP) surveillance of patients with influenza-like illness (ILI) and other acute respiratory infections (ARI). Nose swabs and throat swabs are collected from a subset of patients and tested for influenza virus, RSV, rhinovirus and enterovirus. Furthermore, the weekly reporting of virological laboratory

surveillance by 20 virologic laboratories gives insights in the number of positive RSV tests, reflecting the RSV circulation. These specimens are mainly collected from children [6].

A1.1.1.3 Laboratory data

Laboratory diagnostics are important in monitoring infectious diseases and the effectiveness of vaccination; about 75% of all infectious diseases can only be diagnosed by laboratory tests [7]. However, limited information on patients is registered and, in many cases, laboratory confirmation is not sought for self-limiting vaccine preventable diseases. Two laboratory surveillance systems used for NIP disease surveillance are the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) and the virological laboratories, which are part of the Dutch working Group for Clinical Virology.

A1.1.1.3.1 Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM)

The NRLBM 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 sterile sites (e.g. blood and cerebrospinal fluid (CSF)) of patients with invasive meningococcal disease, invasive pneumococcal disease, and invasive *Haemophilus influenzae* disease to the NRLBM for further typing.
For invasive meningococcal disease and invasive *Haemophilus influenzae* disease, clinical laboratories in the Netherlands send in all invasive (i.e. from normally sterile sites) isolates. For invasive pneumococcal disease, all clinical laboratories send in all positive isolates from CSF. Since 2004, nine sentinel clinical laboratories spread across the country, send in all invasive isolates positive for Streptococcus pneumoniae. These nine sentinel laboratories cover approximately 25% of the Dutch population. Since 2008, for children aged under 5, all clinical laboratories send in all invasive isolates positive for Streptococcus pneumoniae. Besides positive isolates, normally sterile PCR positive material, e.g. CSF or blood, can also be sent to the NRLBM for further typing. This means that we have nationwide laboratory surveillance for invasive meningococcal disease and invasive *Haemophilus influenzae* disease. From 2004 onwards, we have sentinel surveillance for invasive pneumococcal disease covering 25% of the Dutch population for all ages. From 2008 onwards, we have nationwide surveillance for invasive pneumococcal disease for children aged under 5.

A1.1.1.3.2 Virological laboratories

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

A1.1.1.4 *Dedicated studies*

In addition to the data sources described above, dedicated disease surveillance studies are performed to collect data on hospitalisation or mortality. For example, every 2-4 years, clinical data for invasive pneumococcal disease (including mortality and comorbidity) are collected retrospectively from the patient dossiers [8]. Furthermore, retrospective studies were performed to collect disease surveillance data for invasive Hib disease, invasive meningococcal disease, and varicella zoster [9-11].

A1.1.1.5 *Validity of the different data sources*

Data from registers on mortality and hospitalisation are not always reliable. For example, tetani cases are sometimes incorrectly registered as tetanus [5] 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 [12]. Thus, for poliomyelitis and tetanus, notifications are a more reliable source of surveillance.
Additionally, for invasive *Haemophilus influenzae* disease, invasive pneumococcal disease, and, to a lesser extent, invasive meningococcal disease, data on mortality and hospital admissions based on registration databases are unreliable. This is because these are syndromic diseases (meningitis, sepsis and pneumonia) and the causative pathogen is not always correctly specified when these diseases are coded. Notification data in combination with laboratory data from the NRLBM are more reliable for these diseases.
For Rotavirus (RV) disease, there is a specific ICD code available (ICD-9: 008.61, ICD-10: A08.0). However, this code is hardly used in the Netherlands, as more general ICD categories are felt to suffice. Moreover, gastroenteritis hospitalisations are often not tested in general for all causative pathogens, in particular in very young children. For this reason, the number of gastroenteritis hospitalisations attributable to RV is estimated indirectly according to a method proposed by Harris et al. [13]. Using this method, the proportion of hospitalisations for gastroenteritis attributable to RV can be estimated by comparing the weekly RV laboratory detections (surveillance virological laboratories) with the number of hospitalisations for specific gastroenteritis ICD-codes using linear regression analysis (ICD-9: 86-93, 5589; ICD-10: A0,-A09, K52, K529). This linear regression model estimates a constant representing the background number of events for gastroenteritis other than RV infection, and a constant scaling factor dependent on the weekly varying number of RV-positive laboratory detections. The number of hospital admissions attributable to RV infection is calculated from the scaling factor times the number of positive laboratory detections per week. For this report, the constant and scaling factor were estimated by fitting the model on hospitalisation data and weekly laboratory detections (laboratory surveillance) for the five previous years. The scaling factor estimated by this model was used to estimate the RV-attributed hospital admissions for the most recent year by multiplying it with the RV-positive laboratory detections of that year. Because hospitalisation data is available until 2015, the estimates from 2015 are based on the five previous years (2010-2014).
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 have been calculated using an adjusted procedure: changes were made to the definitions of episodes and to calculations of incidence, which caused an increased incidence for many diseases. Episode duration is defined as the time between the first and last consultation registered with the same code, plus an additional period in which patients are considered not susceptible (eight weeks for acute morbidities/complaints). Incidence rates are calculated by using a more specific selection of patient years [14]. Because of these changes, we decided to report previously published incidence rates until 2011 based on the old method [15] and incidence rates from 2012 onwards using the new method [16]. Due to the new estimation method, the data for 2012 (based on 219 practices) and onwards is not comparable with that of previous years.

A1.1.2 Methods for disease surveillance

11.1.2.1 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 between 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 [17, 18].

A1.1.2.2 Impact of implementation of vaccination

Impact of vaccination (programs) can be estimated by comparing disease burden after implementation to disease burden before implementation of vaccination. This can be done quite simply by a before-after comparison of incidence. A more complex alternative is by applying time series analysis, in which, for example, time trends before implementation of vaccination, seasonality and vaccination coverage can be taken into account. For estimating impact of a vaccination program, vaccination status of individuals is not needed; the vaccination coverage of the population suffices. In addition to the effectiveness of the vaccination itself, vaccination coverage and the level of herd protection determine the impact of a vaccination program.

A1.1.2.3 Vaccine effectiveness

To estimate vaccine effectiveness, the vaccination status of at least the cases is necessary. 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 [19]. A specific type of case-control design used to estimate VE is the indirect cohort design or Broome method [20]. This design can be used for a vaccine that protects against specific types of a pathogen, e.g. 10-valent pneumococcal conjugate vaccine,

which protects against 10 pneumococcal serotypes. Cases in which the disease is caused by a vaccine type are the 'cases' and cases in which the disease is caused by a type not included in the vaccine serve as 'controls'. Vaccination status is then compared between the 'cases' (vaccine-type cases) and 'controls' (non-vaccine-type cases). The advantage of this design is that it adjusts for ascertainment bias between cases and controls, as both cases and controls are actually diseased. An assumption made for this design is that vaccinated people are at the same risk of non-vaccine-type infection as unvaccinated people. This means that the VE is underestimated in the case of cross-protection of the vaccine against non-vaccine-type disease. Conversely, if replacement disease occurs only in vaccinated people, the VE is overestimated.
Multiple statistical approaches are available to evaluate the VE against persistent HPV infections through the use of cohort studies. These approaches differ with respect to their underlying assumptions [21]. Based on available literature, no violations of the underlying assumptions, and the use of data throughout the follow-up, we suggest the Prentice Williams Peterson Total-Time (PWP-TT) approach as being most valid for the evaluation of the vaccine effectiveness against HPV infections in cohort studies conducted among young women. The PWP-TT is a survival analysis method for recurrent events, taking into account the total time at risk. It assumes event-specific hazards, allowing the hazard to be different for each subsequent event [22]. We estimated the VE as one minus the hazard ratio times 100%. If the VE is estimated against a combined endpoint of multiple HPV types, then instead of the total number of infections, being infected with one of these types at that time point is used as outcome.

A1.2 Molecular surveillance of the pathogen

The monitoring of strain variations due to differences in phenotype and/or genotype is an important part of information gathering on the emergence of (sub)types that may be more virulent or less effectively controlled by vaccination. It is also a useful tool for increasing insights into transmission dynamics.

A1.3 Immunosurveillance

Monitoring the seroprevalence of all NIP-targeted diseases is a way to gather age specific and sex-specific information on immunity to these diseases, acquired either through natural infection or vaccination. To achieve this, a random selection of people from the general population of the Netherlands is periodically asked to donate a blood sample and to fill in a questionnaire (PIENTER survey). This survey was performed in 1995-1996 (N_{blood}=10,128) [23], in 2006–2007 (N_{blood}=7,904) [24] and in 2016-2017 (N_{blood}=5,745). People living in regions with low vaccine coverage and non-Western migrants are oversampled in order to gain greater insights into differences in immunity among specific groups.

A1.4 Vaccination coverage

Vaccination coverage data can be used to gain insights 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) [25].

A1.5 Surveillance of adverse events following vaccination

Passive safety surveillance through an enhanced spontaneous reporting system was operated by the RIVM until 2011. An aggregated analysis of all reported adverse events following immunisation (AEFI) was published annually. The last report, for 2010, also contains a detailed description of the methodology used and a review of trends and important findings over the previous 15 years [26].

On 1 January 2011, this enhanced spontaneous reporting system of AEFI was taken over by the Netherlands Pharmacovigilance Centre (Lareb). Detailed information is available at *www.lareb.nl*. In view of this transition, comparisons between the period before 2011 and the period running from 2011 onwards should be made with caution. Furthermore, in 2011, Lareb started a campaign among parents of vaccinated children to promote the reporting of AEFIs. From January 2017, registering AEFIs is in the Lareb database has been changed. Previously, a report of redness, swelling, pain and warmth at the injection site were recorded as an injection site inflammation. From January 2017 these local reactions are registered separately. As a result, the number of AEFIs per report is increased.
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.

A1.6 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, compared to 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, 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 cost-effectiveness can contribute to policy recommendations for vaccinations included in the NIP.

A1.7 Literature

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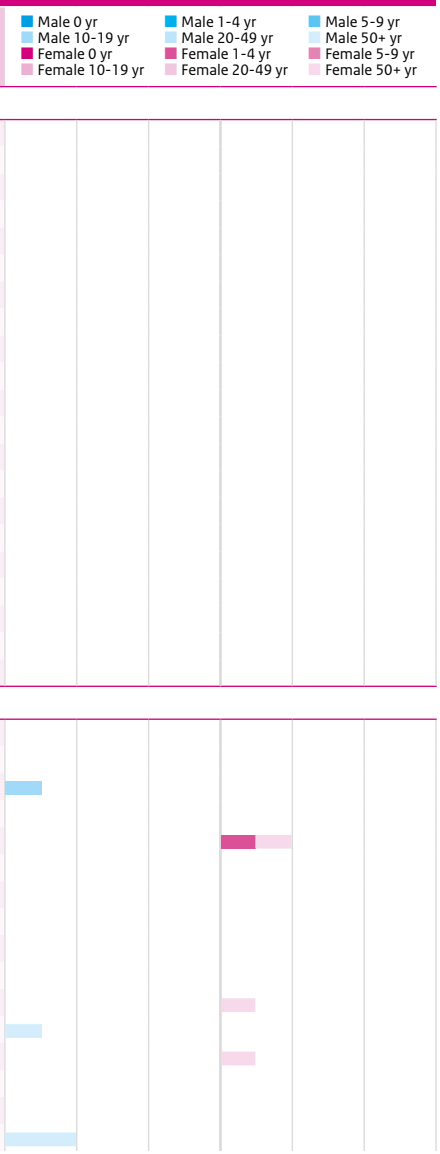
* RIVM publication

Appendix 2 Morbidity and mortality figures

Diseases included in the current NIP

Diphtheria							ICD10: A36
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
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**
2015	0	0	0	0	0	0	**0**
2016	0	0	0	0	0	0	**0**
2017*	0	0	0	0	0	0	**0**
*Hospitalisations** (source: Prismant/DHD)*							
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	2	**2**



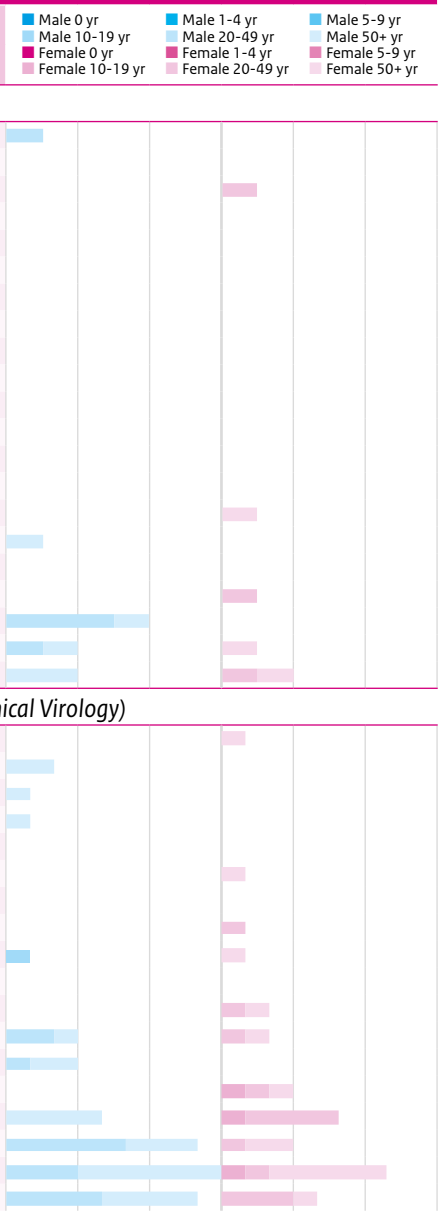
* Preliminary figures. Starting with statistical year 2013, the coding of the causes of death is partly automatic.

** Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system. Hospitalisation data since 2015 are not yet available.

Diphtheria

ICD9: 032
ICD10: A36

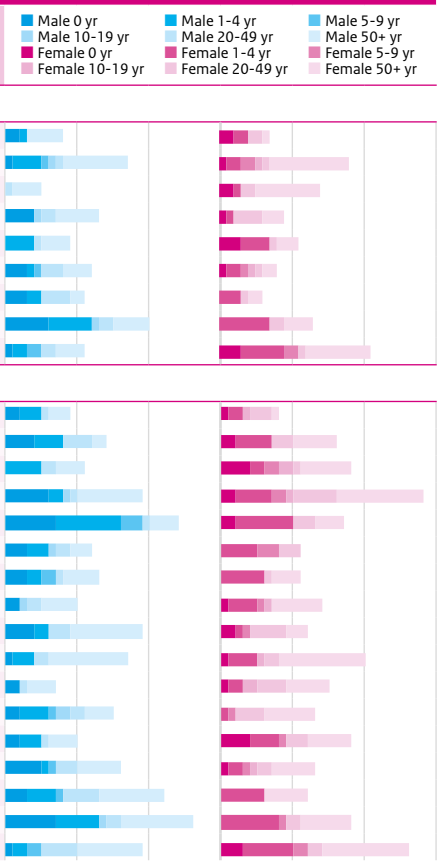
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Notifications (source: Osiris)							
1997	0	0	0	0	1	0	**1**
1998	0	0	0	0	0	0	**0**
1999	0	0	0	0	1	0	**1**
2000	0	0	0	0	0	0	**0**
2001	0	0	0	0	0	0	**0**
2002	0	0	0	0	0	0	**0**
2003	0	0	0	0	0	0	**0**
2004	0	0	0	0	0	0	**0**
2005	0	0	0	0	0	0	**0**
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**
2015	0	0	0	0	3	1	**4**
2016	0	0	0	0	1	2	**3**
2017	0	0	0	0	1	3	**4**
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)*							
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**
2015	0	0	0	0	6	5	**11**
2016	0	0	0	1	5	10	**16**
2017	0	0	0	0	7	5	**12**



*Number of diphtheria isolates.

Haemophilus influenzae

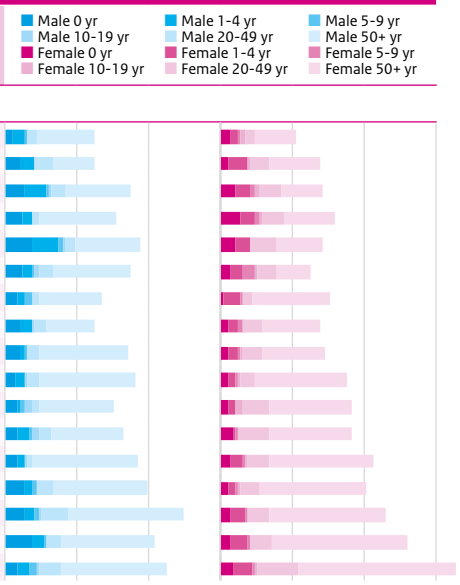
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Notifications (serotype b; source: Osiris)*							
2009	4	3	0	0	2	6	**15**
2010	2	6	3	2	2	20	**35**
2011	2	1	0	0	3	13	**19**
2012	5	1	0	1	6	9	**22**
2013	3	8	0	0	2	7	**20**
2014	4	3	2	1	4	6	**20**
2015	3	5	0	0	5	4	**17**
2016	6	13	0	1	4	9	**33**
2017	4	8	4	0	3	13	**32**
Laboratory diagnoses (serotype b; source: NRLBM)							
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	6	3	2	1	6	12	**30**
2015	3	10	1	0	5	15	**34**
2016	7	14	1	1	4	17	**44**
2017	4	10	4	0	7	21	**46**



*Notifiable since 2009

Haemophilus influenzae

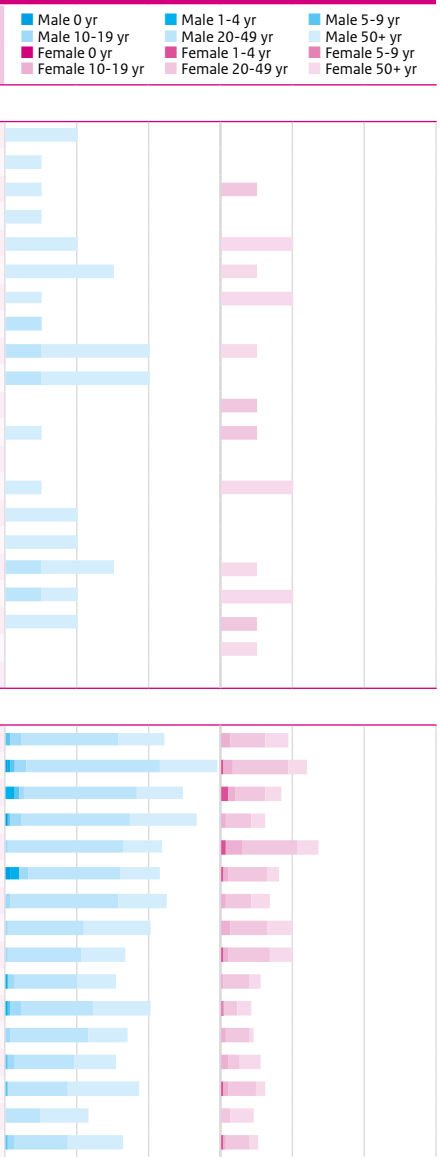
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Laboratory diagnoses (all serotypes; source: NRLBM)							
2001	9	13	2	3	11	55	93
2002	13	18	0	2	22	53	108
2003	21	19	5	4	20	60	129
2004	19	14	2	3	15	72	125
2005	21	24	3	1	19	64	132
2006	14	12	8	4	21	61	120
2007	7	14	5	1	9	79	115
2008	11	14	2	3	18	60	108
2009	11	8	3	2	18	87	129
2010	8	10	1	3	15	106	143
2011	11	6	3	6	20	93	139
2012	12	11	2	4	26	85	140
2013	11	11	2	2	16	117	159
2014	16	6	5	1	22	111	161
2015	15	14	4	1	27	129	190
2016	19	16	2	1	22	130	190
2017	12	20	6	3	34	149	224



Hepatitis B

ICD9: 070.2-3
ICD10: B16, B17.0, B18.0, B18.1

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (B16: Acute; source: CBS)							
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
2015	0	0	0	0	1	2	3
2016	0	0	0	0	0	1	1
2017*	0	0	0	0	0	0	0
*Hospitalisations** (source: Prismant/DHD)*							
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



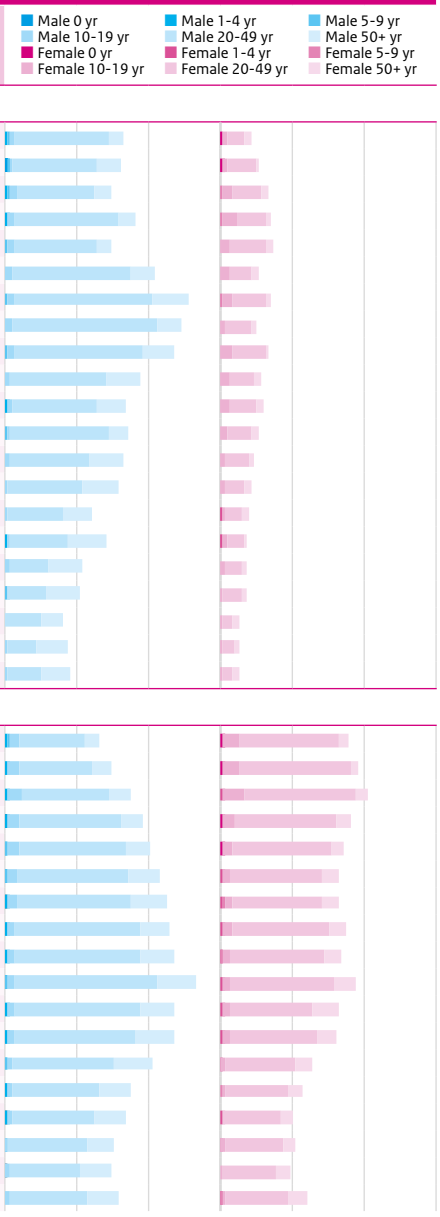
*Preliminary figures. From the statistical year 2013, the coding of the causes of death is partly automatic.

**Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system. Hospitalisation data since 2015 are not yet available.

**For 18 patients, their age is unknown.

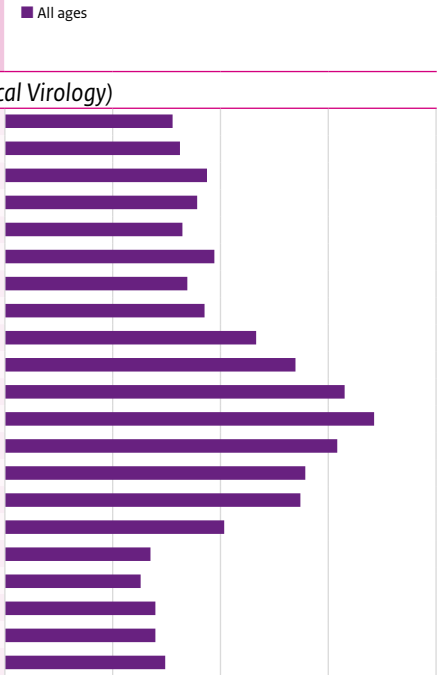
Hepatitis B

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Notifications (Acute; source: Osiris)							
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
2015	0	0	0	1	64	40	105
2016	0	0	0	5	55	51	111
2017	0	0	0	3	62	50	115
Notifications (Chronic; source: Osiris)							
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	788	247	1,075
2015	0	1	1	31	758	226	1,017
2016	1	0	0	36	674	269	980
2017	0	1	1	37	797	269	1,105



Hepatitis B

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)							
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							**1,403**
2011							**1,377**
2012							**1,024**
2013							**677**
2014							**632**
2015							**708**
2016							**708**
2017							**755**



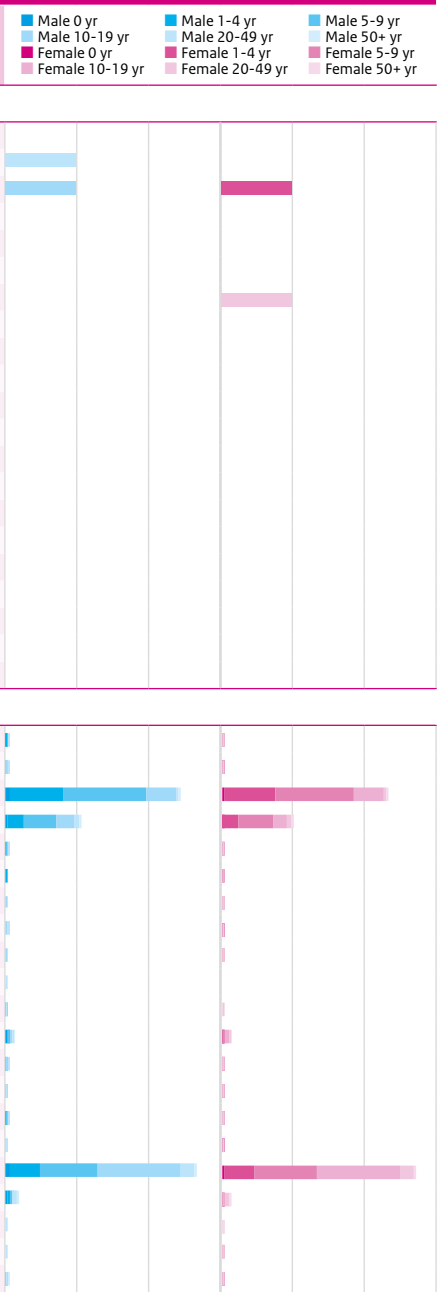
Human papillomavirus								ICD10: C53
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (cervical cancer; source: CBS)								
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	176	**223**	
2014	0	0	0	0	50	148	**198**	
2015	0	0	0	0	49	158	**207**	
2016	0	0	0	0	50	179	**229**	
2017*	0	0	0	0	44	162	**206**	
Registrations (cervical cancer; source NKR)								
1997	0	0	0	1	397	337	**735**	
1998	0	0	0	0	401	353	**754**	
1999	0	0	0	1	408	304	**713**	
2000	0	0	0	0	348	338	**686**	
2001	0	0	0	0	334	272	**606**	
2002	0	0	0	0	334	316	**650**	
2003	0	0	0	0	325	292	**617**	
2004	0	0	0	1	375	327	**703**	
2005	0	0	0	0	363	321	**684**	
2006	0	0	0	0	370	320	**690**	
2007	0	0	0	0	415	327	**742**	
2008	0	0	0	0	376	327	**703**	
2009	0	0	0	0	385	339	**724**	
2010	0	0	0	0	397	339	**736**	
2011	0	0	0	0	388	356	**744**	
2012	0	0	0	1	406	328	**735**	
2013	0	0	0	0	379	284	**663**	
2014	0	0	0	0	416	320	**736**	
2015	0	0	0	0	385	321	**706**	
2016	0	0	0	0	427	332	**759**	
2017**	0	0	0	1	449	367	**817**	

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

**Preliminary figures

Measles — ICD10: B05

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
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**
2015	0	0	0	0	0	0	**0**
2016	0	0	0	0	0	0	**0**
2017*	0	0	0	0	0	0	**0**
Notifications (source: Osiris)							
1997	1	9	0	0	11	0	**21**
1998	1	1	2	2	3	0	**9**
1999	41	738	1,112	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	1,162	199	9	**2,688**
2014	18	25	6	17	65	1	**134**
2015	0	0	0	0	6	1	**7**
2016	0	0	2	0	4	0	**6**
2017	0	1	1	3	10	1	**16**



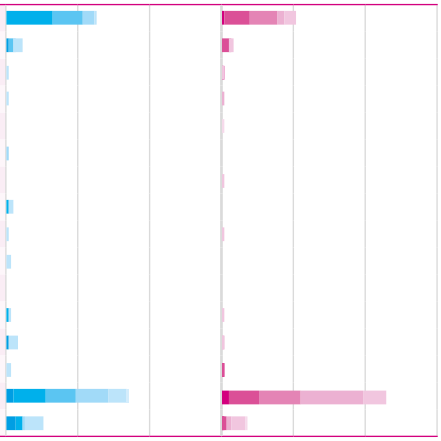
*Preliminary figures. From the statistical year 2013, the coding of the causes of death is partly automatic.

Measles

ICD9: 055
ICD10: B05

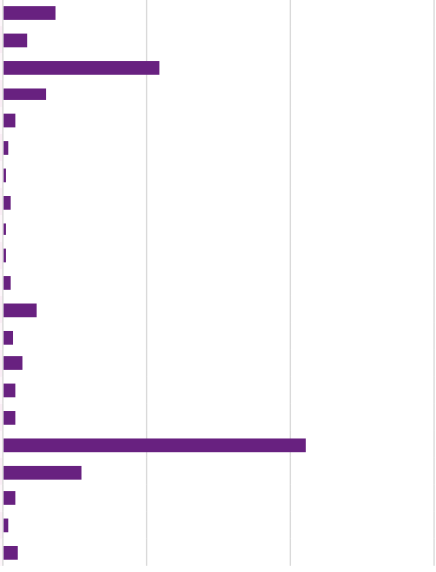
Hospitalisations (source: Prismant/DHD)*

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
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 (source: Dutch Working Group for Clinical Virology)

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	**55**
2015	**8**
2016	**4**
2017	**10**

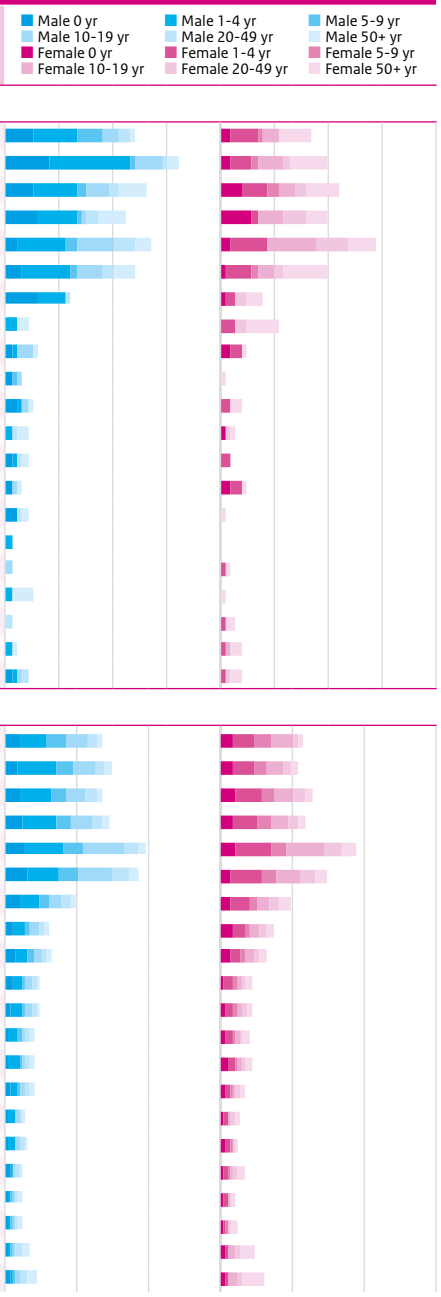


*Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system. Hospitalisation data since 2015 are not yet available.

*For six patients, the age is unknown.

Meningococcal disease — ICD10: A39

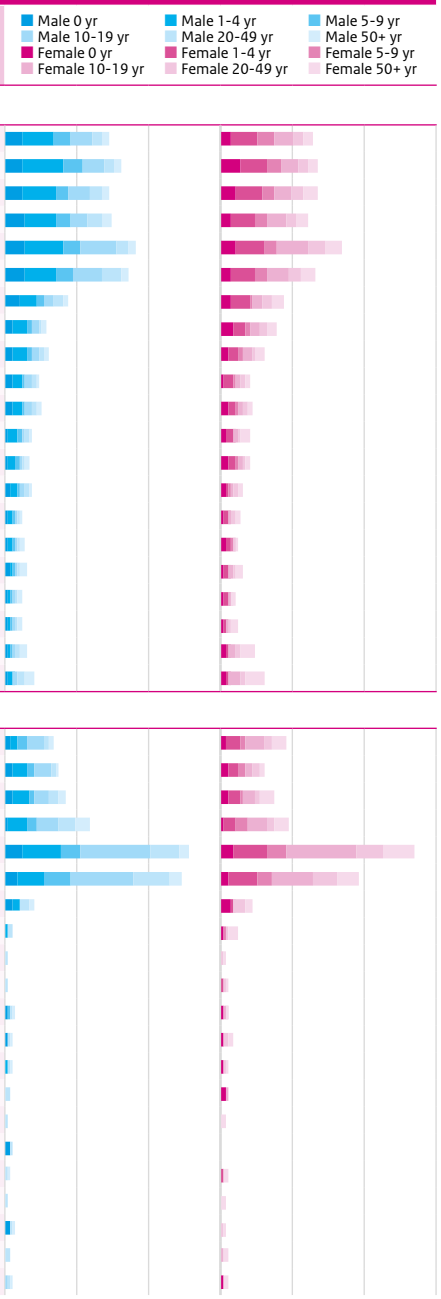
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
1997	7	13	6	6	2	7	**41**
1998	10	19	2	10	2	9	**52**
1999	9	13	4	7	4	11	**48**
2000	12	8	1	6	6	9	**42**
2001	4	16	2	16	10	8	**56**
2002	4	14	2	8	4	12	**44**
2003	7	7	0	0	3	3	**20**
2004	0	5	0	0	2	8	**15**
2005	3	3	0	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**
2015	0	1	0	0	1	2	**4**
2016	0	2	0	1	0	3	**6**
2017*	1	2	0	1	2	2	**8**
Notifications (source: Osiris)							
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	32	6	15	17	16	**104**
2013	16	22	6	14	20	32	**110**
2014	10	17	9	14	10	22	**83**
2015	13	10	9	13	14	33	**92**
2016	13	17	8	27	33	58	**156**
2017	18	22	3	41	34	87	**205**



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

Meningococcal disease

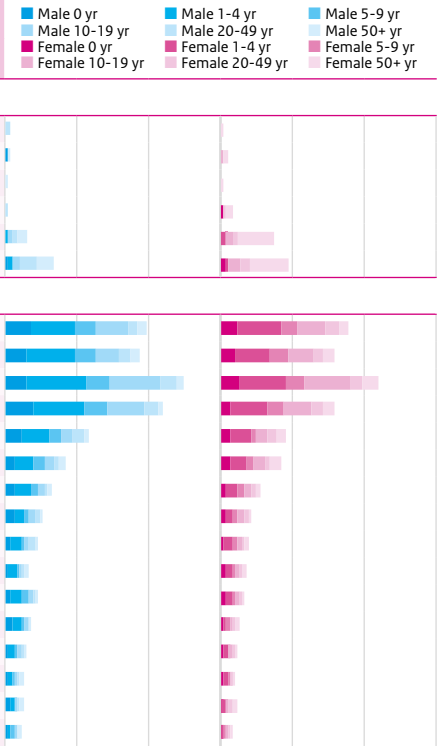
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Laboratory diagnoses (all serogroups; source: NRLBM)							
1997	75	164	101	123	59	46	**568**
1998	101	195	94	117	60	46	**613**
1999	88	175	71	110	66	57	**567**
2000	79	161	73	102	67	62	**544**
2001	91	197	82	194	86	69	**719**
2002	79	154	84	148	86	62	**613**
2003	61	98	37	54	56	45	**351**
2004	50	75	27	45	31	43	**271**
2005	41	63	29	45	30	34	**242**
2006	25	49	22	32	23	24	**175**
2007	30	51	20	30	27	28	**186**
2008	15	47	18	18	22	39	**159**
2009	25	47	18	23	16	28	**157**
2010	23	34	13	18	21	28	**137**
2011	15	23	4	18	19	22	**101**
2012	18	28	7	11	17	16	**97**
2013	19	21	6	15	19	37	**117**
2014	10	16	10	12	11	23	**82**
2015	12	10	5	14	15	33	**89**
2016	14	15	7	24	28	63	**151**
2017	16	21	3	41	35	82	**198**
Laboratory diagnoses (serogroup C; source: NRLBM)							
1997	6	16	11	25	8	14	**80**
1998	9	17	11	17	8	6	**68**
1999	9	20	5	21	10	16	**81**
2000	2	22	16	29	19	19	**107**
2001	20	53	27	105	43	29	**277**
2002	13	39	30	73	42	25	**222**
2003	11	6	0	1	16	8	**42**
2004	1	1	1	0	7	7	**17**
2005	0	0	0	0	2	2	**4**
2006	0	1	0	0	2	1	**4**
2007	2	0	1	1	4	2	**10**
2008	2	0	0	0	4	5	**11**
2009	1	1	0	0	2	5	**9**
2010	2	0	0	2	2	0	**6**
2011	0	0	0	0	1	2	**3**
2012	2	0	0	0	1	0	**3**
2013	0	1	0	0	1	4	**6**
2014	0	0	0	0	1	2	**3**
2015	2	0	0	0	3	3	**8**
2016	0	0	0	1	2	3	**6**
2017	1	0	0	1	1	6	**9**



Meningococcal disease

ICD9: 036.0-4, 036.8-9
ICD10: A39

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Laboratory diagnoses (serogroup W; source: NRLBM)							
2012	0	0	0	0	2	1	**3**
2013	1	0	0	1	0	5	**7**
2014	0	0	0	0	0	2	**2**
2015	1	0	0	0	2	6	**9**
2016	0	3	1	8	7	31	**50**
2017	4	4	0	15	18	39	**80**
Hospitalisations (source: Prismant/DHD)*							
1999	114	251	98	170	66	53	**755**
2000	98	233	109	132	64	55	**694**
2001	114	295	113	268	85	66	**949**
2002	106	238	110	182	72	47	**767**
2003	72	135	46	64	57	44	**421**
2004	54	101	46	58	31	45	**336**
2005	45	70	36	45	19	27	**244**
2006	35	50	28	40	20	21	**196**
2007	23	58	17	22	28	18	**166**
2008	18	48	15	14	11	30	**136**
2009	28	49	26	25	14	13	**156**
2010	21	37	12	20	13	18	**122**
2011	18	27	12	20	13	11	**103**
2012	15	26	11	11	9	12	**84**
2013	16	22	4	14	17	25	**99**
2014	10	15	13	11	10	16	**75**

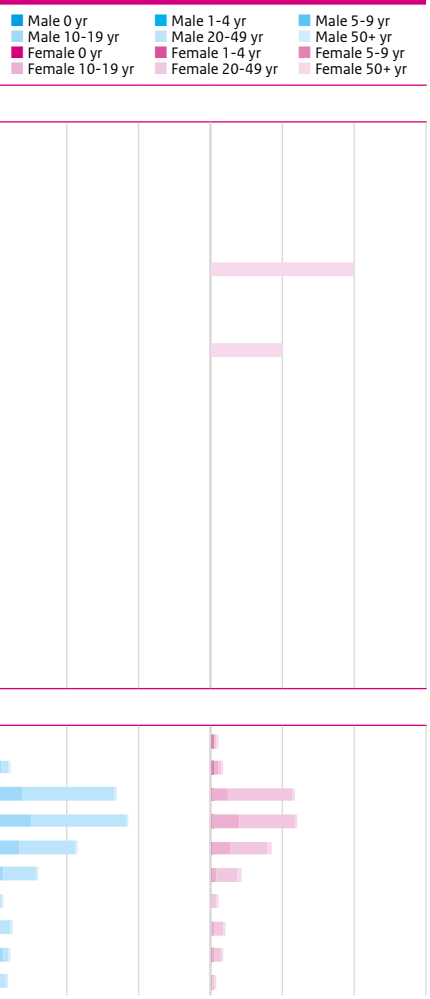


*Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system. Hospitalisation data since 2015 are not yet available.

*For 12 patients, the age is unknown.

Mumps — ICD10: B26

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
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**
2015	0	0	0	0	0	0	**0**
2016	0	0	0	0	0	0	**0**
2017*	0	0	0	0	0	0	**0**
Notifications (source: Osiris)							
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**
2015	0	0	2	21	61	5	**89**
2016	0	5	7	20	34	5	**71**
2017	1	3	0	8	32	2	**46**



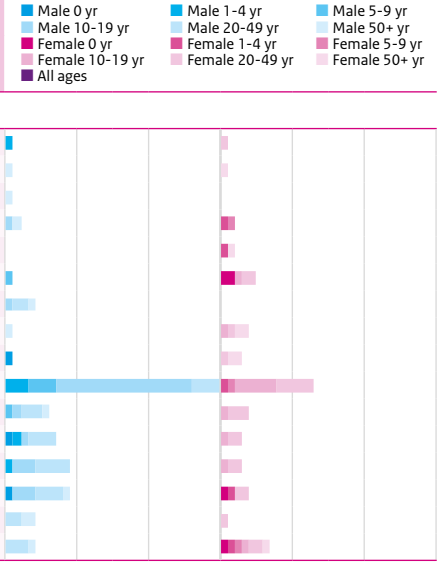
*Preliminary figures. From the statistical year 2013, the coding of the causes of death is partly automatic.

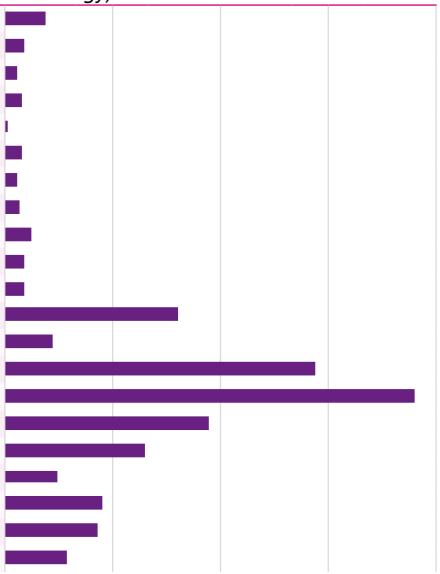
**Notifiable from 1 December 2008 onwards

Mumps

ICD9: 072
ICD10: B26

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Hospitalisations (source: Prismant/DHD)*							
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 (source: Dutch Working Group for Clinical Virology)							
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							**24**
2015							**45**
2016							**43**
2017							**29**





*Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system. Hospitalisation data since 2015 are not yet available.

*For one patient, his/her age is unknown.

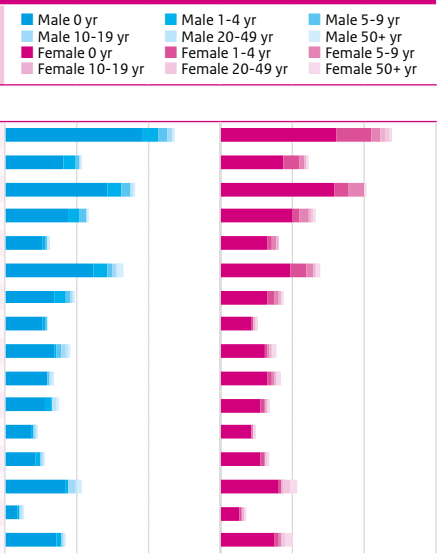
Pertussis								ICD10: A37
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
1997	2	0	0	0	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**	
2015	1	0	0	0	0	0	**1**	
2016	1	0	0	0	0	1	**2**	
2017*	1	0	0	0	0	1	**2**	
Notifications (source: Osiris)								
1997	179	677	867	412	423	130	**2,688**	
1998	123	670	997	344	316	118	**2,568**	
1999	256	1,177	2,627	1,355	1,095	467	**6,977**	
2000	176	757	1,628	677	651	376	**4,265**	
2001	307	1,164	3,400	1,342	1,212	605	**8,030**	
2002	168	511	1,624	1,004	807	438	**4,552**	
2003	134	367	1,070	582	465	245	**2,863**	
2004	367	1,006	2,750	2,390	2,099	1,139	**9,751**	
2005	190	787	1,292	1,586	1,212	850	**5,917**	
2006	143	471	788	1,353	987	622	**4,364**	
2007	190	450	837	2,888	2,057	1,331	**7,753**	
2008	195	346	779	3,154	2,343	1,484	**8,301**	
2009	164	270	658	2,442	1,962	1,064	**6,560**	
2010	115	168	355	1,278	1,212	637	**3,765**	
2011	160	283	1,007	2,531	1,984	1,231	**7,196**	
2012	234	378	1,525	4,192	4,497	3,002	**13,828**	
2013	77	136	315	889	1,054	931	**3,402**	
2014	258	490	788	2,859	2,721	2,138	**9,254**	
2015	174	274	560	1,962	2,053	1,532	**6,555**	
2016	217	402	489	1,426	1,813	1,223	**5,570**	
2017	182	221	416	1,307	1,610	1,146	**4,912**	

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

Pertussis

ICD9: 033
ICD10: A37

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Hospitalisations (source: Prismant/DHD)*							
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	146	11	4	3	7	12	**185**

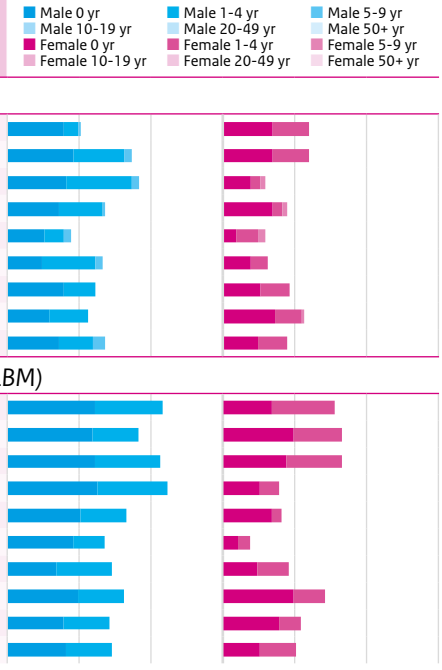


*Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system. Hospitalisation data since 2015 are not yet available.

*For three patients, the age is unknown.

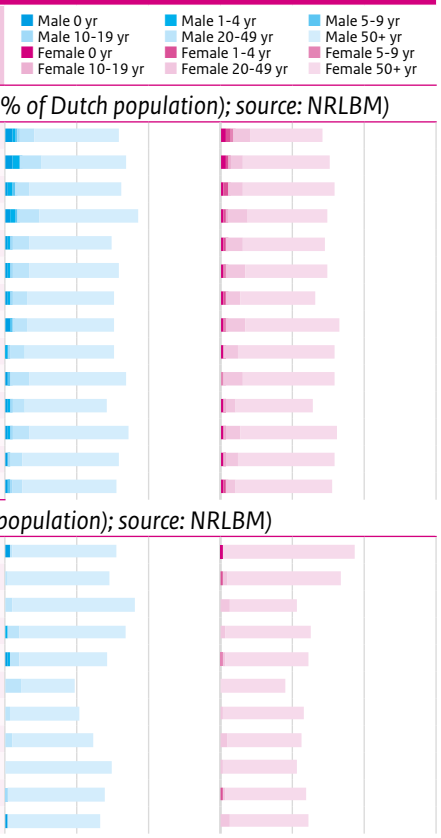
Pneumococcal disease

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Notifications IPD (source: Osiris)*							
2009	27	15	1	0			**43**
2010	31	24	2	0			**57**
2011	23	20	4	0			**47**
2012	26	16	2	0			**44**
2013	11	13	4	0			**28**
2014	16	20	2	0			**38**
2015	25	17	0	0			**42**
2016	25	18	1	0			**44**
2017	23	17	4	1			**45**
Laboratory diagnoses IPD (<5 years, nationwide; source: NRLBM)							
2008	40	40					**80**
2009	45	28					**73**
2010	44	34					**78**
2011	38	26					**64**
2012	33	17					**50**
2013	22	12					**34**
2014	22	25					**47**
2015	38	22					**60**
2016	30	19					**49**
2017	26	24					**50**



Pneumococcal disease

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Laboratory diagnoses IPD (all ages, sentinel labs (covering 25% of Dutch population); source: NRLBM)							
2004	30	20	10	12	88	444	**604**
2005	24	30	3	8	95	480	**640**
2006	11	23	4	4	83	516	**641**
2007	11	24	10	12	110	519	**686**
2008	10	14	4	5	100	474	**607**
2009	8	10	4	10	110	478	**620**
2010	9	12	6	4	83	459	**573**
2011	11	7	8	7	95	506	**634**
2012	4	7	3	3	81	540	**638**
2013	4	3	4	6	110	525	**652**
2014	5	11	5	5	67	454	**547**
2015	10	5	1	9	95	547	**667**
2016	6	5	3	4	66	547	**631**
2017	8	8	5	4	60	531	**616**
Mortality IPD (all ages, sentinel labs (covering 25% of Dutch population); source: NRLBM)							
2005	3	0	0	0	1	101	**105**
2006	0	1	0	0	3	91	**95**
2007	0	0	0	0	7	82	**89**
2008	0	1	0	0	7	82	**90**
2009	1	1	1	0	4	75	**82**
2010	0	0	0	0	6	52	**58**
2011	0	0	0	0	3	65	**68**
2012	0	0	0	0	6	68	**74**
2013	0	0	0	0	1	75	**76**
2014	0	1	0	1	1	75	**78**
2015	1	0	0	0	4	72	**77**

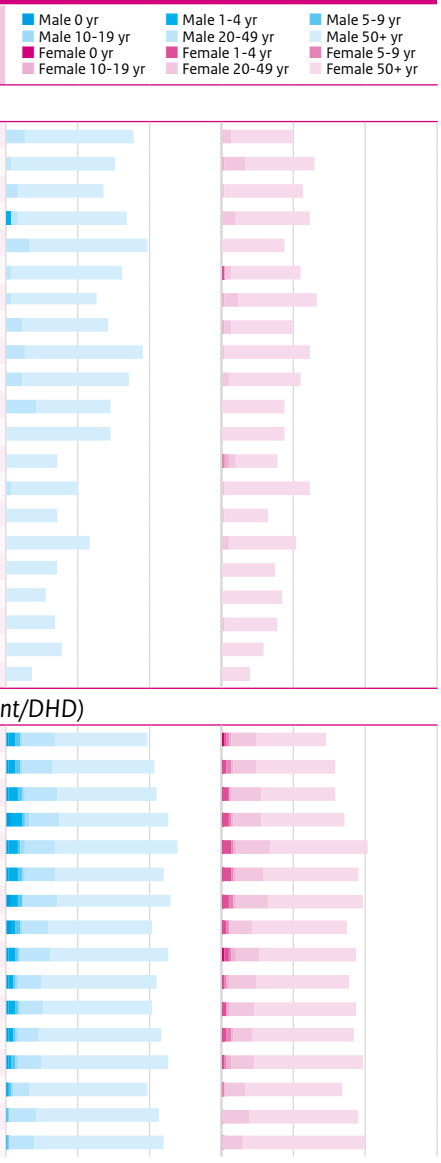


*Notifiable for 0- to 5-year-old children since 2009.

Pneumococcal disease

ICD9: 481
ICD10: J13

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality pneumococcal pneumonia (source: CBS)*							
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	1	0	0	3	50	**54**
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	29	**29**
2014	0	0	0	0	0	28	**28**
2015	0	0	0	0	1	28	**29**
2016	0	0	0	0	0	27	**27**
2017*	0	0	0	0	0	15	**15**
*Hospitalisations pneumococcal pneumonia** (source: Prismant/DHD)*							
1999	35	74	48	37	394	1,126	**1,719**
2000	32	75	48	41	360	1,257	**1,817**
2001	24	102	39	34	421	1,215	**1,839**
2002	45	123	41	35	414	1,323	**1,987**
2003	28	115	34	49	454	1,523	**2,215**
2004	33	103	51	37	409	1,416	**2,051**
2005	29	95	57	36	461	1,446	**2,130**
2006	25	72	46	28	333	1,388	**1,893**
2007	10	87	41	33	382	1,502	**2,064**
2008	8	68	31	21	352	1,452	**1,938**
2009	28	59	30	36	332	1,465	**1,955**
2010	23	62	37	35	285	1,560	**2,009**
2011	17	40	46	38	337	1,631	**2,111**
2012	4	28	11	20	263	1,506	**1,835**
2013	0	4	7	17	384	1,606	**2,020**
2014	3	4	3	19	309	1,754	**2,095**



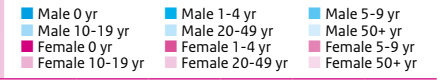
*Preliminary figures. From the statistical year 2013, the coding of the causes of death is partly automatic.

**Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system. Hospitalisation data since 2015 are not yet available.

**For 16 patients, the age is unknown.

Poliomyelitis — ICD10: A80

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (acute; source: CBS)							
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	0	**0**
2014	0	0	0	0	0	0	**0**
2015	0	0	0	0	0	0	**0**
2016	0	0	0	0	0	0	**0**
2017*	0	0	0	0	0	0	**0**
Notifications (source: Osiris)							
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**
2015	0	0	0	0	0	0	**0**
2016	0	0	0	0	0	0	**0**
2017	0	0	0	0	0	0	**0**



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

Poliomyelitis								ICD9: 045 ICD10: A80
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Hospitalisations (source: Prismant/DHD)*								
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 were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system. Hospitalisation data since 2015 are not yet available.

Rubella (acquired) — ICD10: B06

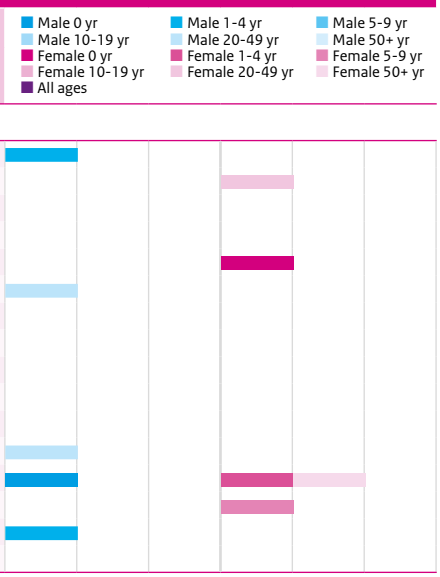
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
1997	0	0	0	0	0	0	**0**
1998	0	0	0	0	0	0	**0**
1999	0	0	0	0	0	0	**0**
2000	0	0	0	0	0	0	**0**
2001	0	0	0	0	0	0	**0**
2002	0	0	0	0	1	0	**1**
2003	0	0	0	0	0	0	**0**
2004	0	0	0	0	0	0	**0**
2005	0	0	0	0	1	0	**1**
2006	0	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**
2015	0	0	0	0	0	0	**0**
2016	0	0	0	0	0	0	**0**
2017*	0	0	0	0	0	0	**0**
Notifications (source: Osiris)							
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**
2015	0	0	0	0	1	0	**1**
2016	0	0	0	0	0	0	**0**
2017	0	0	0	0	0	0	**0**

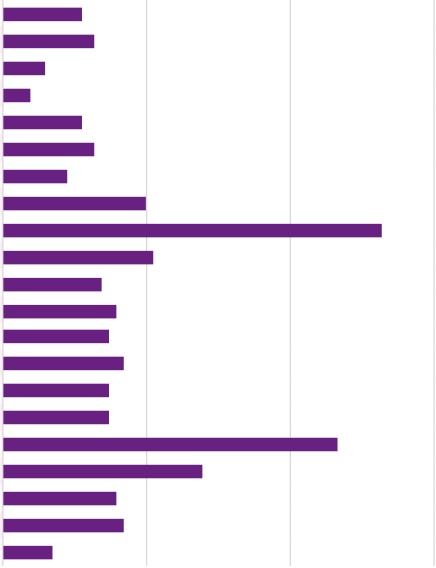
*Preliminary figures. From the statistical year 2013, the coding of the causes of death is partly automatic.

Rubella (acquired)

ICD9: 056
ICD10: B06

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Hospitalisations (source: Prismant/DHD)*							
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 (source: Dutch Working Group for Clinical Virology)***							
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**
2015							**16**
2016							**17**
2017							**7**





*Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system. Hospitalisation data since 2015 are not yet available.

** The numbers can be higher than the notifications as false-positive results or cases not meeting the notification criteria can be included.

Tetanus								ID10: A33-35
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
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**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
1997	0	0	0	0	1	3	**4**	
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**	
2015	0	0	0	1	0	0	**1**	
2016	0	0	0	0	0	1	**1**	
2017	0	0	0	0	0	1	**1**	

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

**No notifications in 1999–2008

Potential NIP target diseases

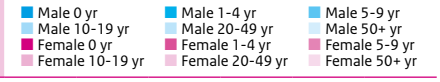
Hepatitis A								ICD10: B15
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (acute; source: CBS)								
1997	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**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017*	0	0	0	0	0	0	**0**	

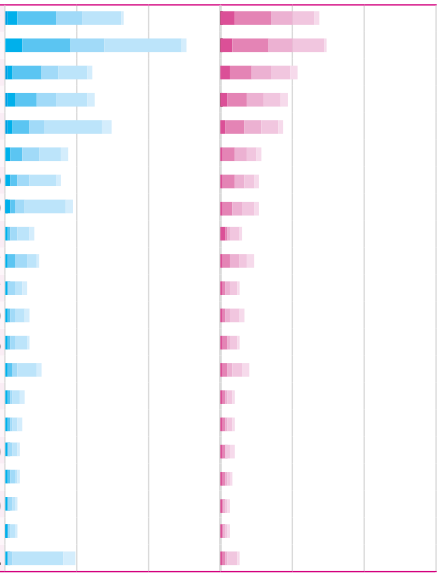
*Preliminary figures. From the statistical year 2013, the coding of the causes of death is partly automatic.

Hepatitis A — ICD10: B15

Notifications (source: Osiris)*

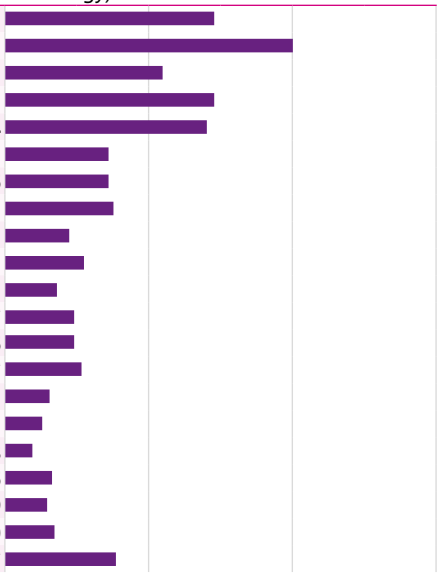
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
1997	3	96	318	199	253	37	**913***
1998	1	114	360	235	446	47	**1,210***
1999	2	58	210	148	217	53	**694***
2000	3	63	174	146	205	54	**647***
2001	2	43	149	126	318	63	**704***
2002	0	22	97	119	144	51	**433**
2003	0	23	81	96	139	50	**389**
2004	1	21	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**
2015	0	8	12	22	28	10	**80**
2016	1	5	12	18	33	12	**81**
2017	0	5	21	31	243	74	**374**





Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)

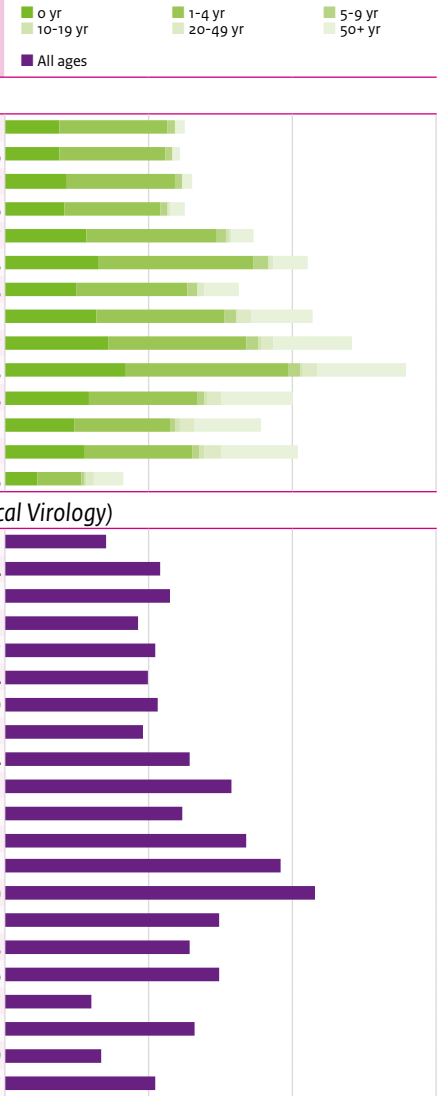
1997	**295**
1998	**405**
1999	**223**
2000	**293**
2001	**284**
2002	**145**
2003	**146**
2004	**153**
2005	**91**
2006	**111**
2007	**72**
2008	**97**
2009	**96**
2010	**107**
2011	**63**
2012	**53**
2013	**38**
2014	**66**
2015	**59**
2016	**70**
2017	**157**



*For 25 patients, their age is unknown.

Rotavirus

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Hospitalisations (estimation; source: Prisman/DHD)*							
2001	1,154	2,277	147	0	0	184	**3,762**
2002	1,180	2,208	148	0	0	160	**3,696**
2003	1,298	2,287	160	0	0	202	**3,947**
2004	1,240	2,011	160	16	51	298	**3,776**
2005	1,729	2,744	199	19	83	443	**5,217**
2006	1,990	3,254	272	26	109	737	**6,388**
2007	1,532	2,323	189	23	139	722	**4,928**
2008	1,933	2,702	211	47	274	1,288	**6,455**
2009	2,171	2,924	220	45	301	1,636	**7,297**
2010	2,534	3,398	262	60	329	1,845	**8,428**
2011	1,754	2,294	167	56	305	1,502	**6,078**
2012	1,470	1,985	148	71	329	1,392	**5,395**
2013	1,682	2,270	169	81	377	1,592	**6,171**
2014	686	927	69	33	153	650	**2,518**
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)							
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							**1,935**
2010							**2,180**
2011							**1,505**
2012							**1,288**
2013							**1,496**
2014							**607**
2015							**1,323**
2016							**679**
2017							**1,047**

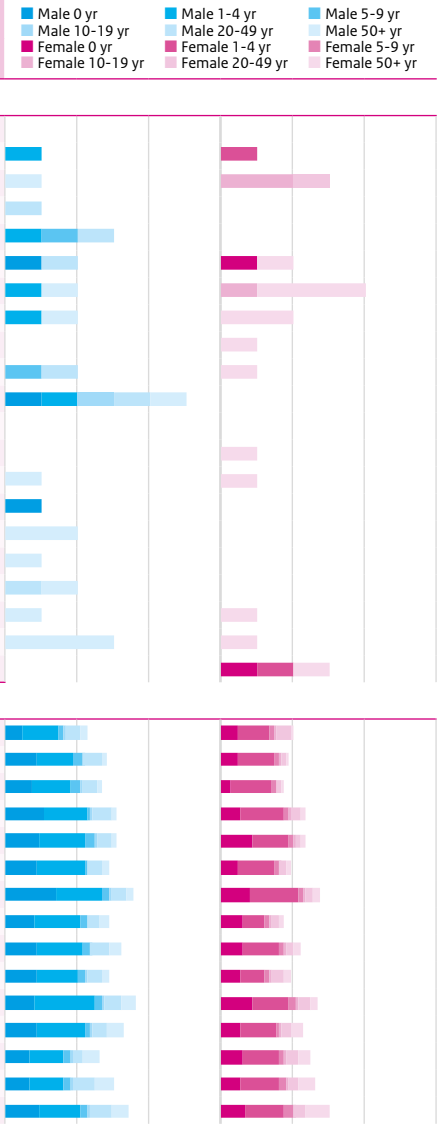


*Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system. Hospitalisation data since 2015 are not yet available; therefore.

Varicella (chickenpox)

ICD9: 052
ICD10: B01

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
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**
2015	0	0	0	0	0	2	**2**
2016	0	0	0	0	0	4	**4**
2017*	1	1	0	0	0	1	**3**
*Hospitalisations** (source: Prismant/DHD)*							
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	76	112	22	6	49	56	**321**



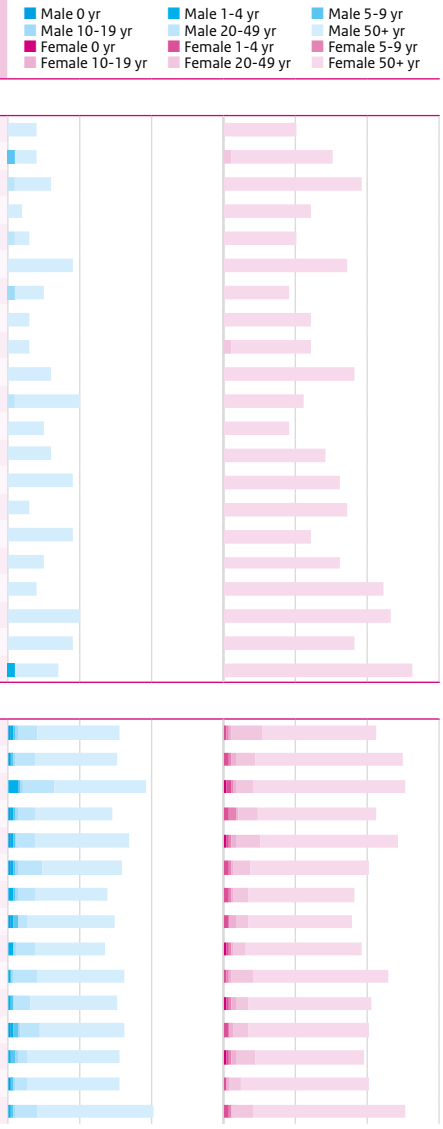
*Preliminary figures. From the statistical year 2013, the coding of the causes of death is partly automatic.

**Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

Herpes zoster (shingles)

ICD9: 053
ICD10: B02

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
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**
2015	0	0	0	0	0	33	**33**
2016	0	0	0	0	0	27	**27**
2017*	0	1	0	0	0	32	**33**
*Hospitalisations** (source: Prismant/DHD)*							
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	58	373	**451**



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

**Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onward, diseases have been coded according to the ICD-10 coding system.

Appendix 3 Overview of vaccin changes in the NIP since 2000

July 2001
→ Acellular pertussis vaccine (GSK)
🕒 4 years of age
Children born on or after 1 January 1998

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

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])

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

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

June 2006
→ Prevnar (Wyeth)
🕒 2, 3, 4 and 11 months of age
Children born on or after 1 April 2006

June 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])

Legend

🕒 ***Age of vaccination***
\+ ***Additional campaign for specific groups of children***

[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.

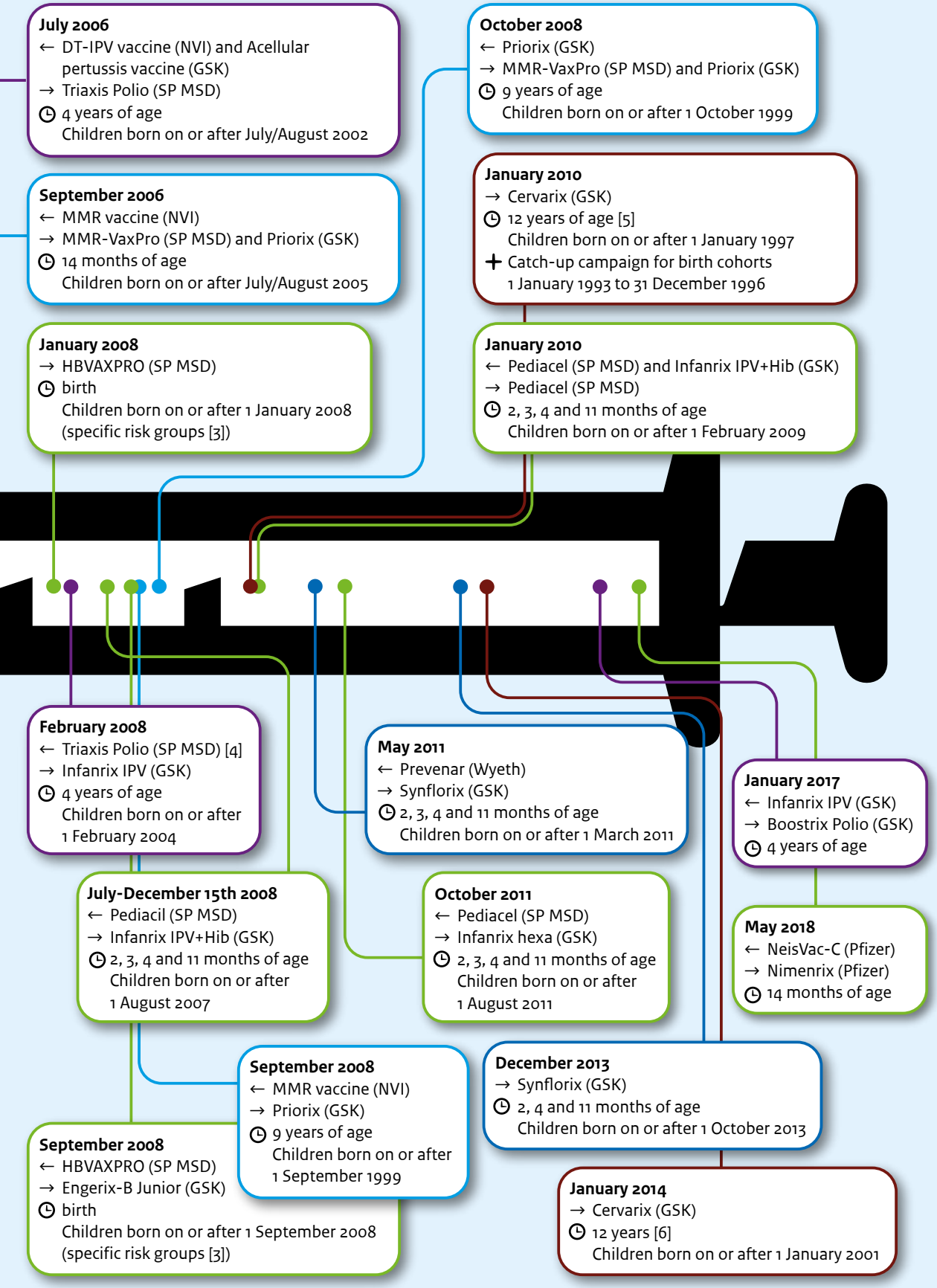
[2] Only for children whose mother tested positive for HBsAg.

[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.


July 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
September 2006
← MMR vaccine (NVI)
→ MMR-VaxPro (SP MSD) and Priorix (GSK)
14 months of age
Children born on or after July/August 2005
January 2008
→ HBVAXPRO (SP MSD)
birth
Children born on or after 1 January 2008
(specific risk groups [3])
October 2008
← Priorix (GSK)
→ MMR-VaxPro (SP MSD) and Priorix (GSK)
9 years of age
Children born on or after 1 October 1999
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
January 2010
← 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
February 2008
← Triaxis Polio (SP MSD) [4]
→ Infanrix IPV (GSK)
4 years of age
Children born on or after 1 February 2004
May 2011
← Prevenar (Wyeth)
→ Synflorix (GSK)
2, 3, 4 and 11 months of age
Children born on or after 1 March 2011
January 2017
← Infanrix IPV (GSK)
→ Boostrix Polio (GSK)
4 years of age
July-December 15th 2008
← Pediacil (SP MSD)
→ Infanrix IPV+Hib (GSK)
2, 3, 4 and 11 months of age
Children born on or after 1 August 2007
October 2011
← Pediacel (SP MSD)
→ Infanrix hexa (GSK)
2, 3, 4 and 11 months of age
Children born on or after 1 August 2011
May 2018
← NeisVac-C (Pfizer)
→ Nimenrix (Pfizer)
14 months of age
September 2008
← MMR vaccine (NVI)
→ Priorix (GSK)
9 years of age
Children born on or after 1 September 1999
December 2013
→ Synflorix (GSK)
2, 4 and 11 months of age
Children born on or after 1 October 2013
September 2008
← HBVAXPRO (SP MSD)
→ Engerix-B Junior (GSK)
birth
Children born on or after 1 September 2008
(specific risk groups [3])
January 2014
→ Cervarix (GSK)
12 years [6]
Children born on or after 1 January 2001

Appendix 4 Composition of vaccines used in the NIP

Vaccine	Composition
M-M-R VaxPro / MSD EU/1/06/337 Mumps, measles and rubella vaccine 0.5 ml	**Mumps virus (Jeryl Lynn) > 12,500 TCID50** (tissue culture infectious doses) Measles virus (Enders' Edmonston) > 1000 TCID50 Rubella virus (Wistar RA 27/3) > 1000 TCID50
Infanrix IPV / GSK RVG 34568 Diphtheria, tetanus, pertussis (acellular component), inactivated poliomyelitis vaccine 0.5 ml	Adsorbed diphtheria toxoid > 30 IU Adsorbed tetanus toxoid > 40 IU Adsorbed pertussis toxoid (PT) 25 µg Adsorbed filamentous haemagglutinin (FHA) 25 µg Absorbed pertactin (PRN) 8 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU
Boostrix Polio / GSK RVG 35124 Diphtheria, tetanus, pertussis (acellular component), inactivated poliomyelitis vaccine (adsorbed, reduced antigen) 0.5 ml	Adsorbed diphtheria toxoid > 2 IU Adsorbed tetanus toxoid > 20 IU Adsorbed pertussis toxoid (PT) 8 µg Adsorbed filamentous haemagglutinin (FHA) 8 µg Absorbed pertactin (PRN) 2.5 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU
Infanrix Hexa / GSK RVG17641 Diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), inactivated poliomyelitis vaccine and conjugated *Haemophilus influenzae* type b-vaccine (adsorbed) 0.5 ml	Adsorbed diphtheria toxoid > 30 IU Adsorbed tetanus toxoid > 40 IU Adsorbed pertussis toxoid (PT) 25 µg Adsorbed filamentous haemagglutinin (FHA) 25 µg Adsorbed pertactin (PRN) 8 µg Adsorbed recombinant HBsAg protein 10 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU Adsorbed purified capsular polysaccharide of Hib (PRP) 10 µg covalently bound to tetanus toxoid (T) 20–40 µg

Vaccine	Composition
REVAXIS / SP RVG24534 Diphtheria, tetanus and inactivated poliomyelitis vaccine (absorbed; limited quantity of antigen(s)) 0.5 ml	Purified diphtheria-toxoid* > 2 IU Purified tetanus toxoid* > 20 IU Inactivated poliovirus type 1** 40 DU Inactivated poliovirus type 2** 8 DU Inactivated poliovirus type 3** 32 DU *adsorbed to aluminiumhydroxide 0.35 mg **produced on Verocells
Engerix-B Junior / GSK RVG24290 Hepatitis B vaccine (recombinant) 0.5 ml	Hepatitis B-virus surface antigen, recombinant* (S protein) absorbed 10 µg *produced on genetically engineered yeast cells (Saccharomyces cerevisiae)
HBVAXPRO / MSD RVG17316 Hepatitis B vaccine (rDNA) 0.5 ml	Hepatitis B virus surface antigen, recombinant (HBsAg)[1,2] 5 µg [1] Adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.25 mg Al+) [2] Produced in Saccharomyces cerevisiae (strain 2150-2-3) yeast by recombinant DNA technology
Act-HIB / SP *Haemophilus influenza* type b Conjugate Vaccine (Tetanus Protein - Conjugate) 0.5 ml	Purified polyribose ribitol phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b[1] 10 µg [1] covalently bound to tetanus protein 20 µg
Cervarix / GSK EU/1/07/419	Human papillomavirus type 16 L1 protein[2,3,4] 20 µg Human papillomavirus type 18 L1 protein[2,3,4] 20 µg [1] adjuvanted by AS04 containing 3-O-desacyl-4'-monophosphoryl lipid A (MPL)[3] 50 µg [2] absorbed on aluminium hydroxide, hydrated (Al(OH)3) 0.5 mg AL^{3+} in total [3] L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system which uses Hi-5 Rix4446 cells derived from *Trichoplusia ni*.
Nimenrix / Pfizer EU/1/12/767 Conjugated meningococcal group A, C, W-135 and Y vaccine 0.5 ml	*Neisseria meningitidis*-group A polysaccharide[1] 5 µg *Neisseria meningitidis*-group C polysaccharide[1] 5 µg *Neisseria meningitidis*-group W-135 polysaccharide[1] 5 µg *Neisseria meningitidis*-group Y polysaccharide[1] 5 µg [1]conjugated to tetanus toxoid carrier protein 44 µg

Vaccine	Composition
NeisVac-C / Pfizer RVG26343 Conjugated meningococcal C saccharide vaccine (adsorbed) 0.5 ml	*Neisseria meningitidis* (C11-strain) Polysaccharide O-deacetylated 10 µg conjugated to tetanus toxoid 10-20 µg adsorbed to aluminium hydroxide 0.5 mg Al^{3+}
Synflorix / GSK EU/1/09/508 Pneumococcal polysaccharide conjugate vaccine (adsorbed) 0.5 ml	Pneumococcal polysaccharide serotype 1[1,2] 1 µg Pneumococcal polysaccharide serotype 4[1,2] 3 µg Pneumococcal polysaccharide serotype 5[1,2] 1 µg Pneumococcal polysaccharide serotype 6B[1,2] 1 µg Pneumococcal polysaccharide serotype 7F[1,2] 1 µg Pneumococcal polysaccharide serotype 9V[1,2] 1 µg Pneumococcal polysaccharide serotype 14[1,2] 1 µg Pneumococcal polysaccharide serotype 18C[1,3] 3 µg Pneumococcal polysaccharide serotype 19F[1,4] 3 µg Pneumococcal polysaccharide serotype 23F[1,2] 1 µg [1] absorbed to aluminium phosphate 0.5 mg Al3+ [2] conjugated to protein D (obtained from nontypeable *Haemophilus influenzae*) carrier protein 9–16 mg [3] conjugated to tetanus toxoid 5–10 mg [3] conjugated to diphtheria toxoid 3–6 mg

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

Appendix 5 Overview of recent RIVM publications (01-08-2017 to 31-08-2018)

Vaccination coverage

1. van Lier EA, Geraedts JLE, Oomen PJ, Giesbers H, van Vliet JA, Drijfhout IH, et al. Vaccinatiegraad en jaarverslag Rijksvaccinatieprogramma Nederland 2017. [Vaccination coverage and annual report National Immunisation Programme Netherlands 2017]. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2018 (RIVM report 2018-0008).
2. Bogaards JA, Coupe VM, Xiridou M, Meijer CJ, Wallinga J, Berkhof J. Long-term impact of human papillomavirus vaccination on infection rates, cervical abnormalities, and cancer incidence. Epidemiology. 2011;22(4):505-15.
3. Nic Lochlainn LM, Woudenberg T, van Lier A, Zonnenberg I, Philippi M, de Melker HE, et al. A novel measles outbreak control strategy in the Netherlands in 2013-2014 using a national electronic immunization register: A study of early MMR uptake and its determinants. Vaccine. 2017;35(43):5828-34.

Acceptance of vaccination

1. Fournet N, Mollema L, Ruijs WL, Harmsen IA, Keck F, Durand JY, Cunha MP, Wamsiedel M, Reis R, French J, Smit EG, Kitching A, van Steenbergen JE. Under-vaccinated groups in Europe and their beliefs, attitudes and reasons for non-vaccination; two systematic reviews. BMC Public Health. 2018 Jan 30;18(1):196. doi: 10.1186/s12889-018-5103-8. Review. PubMed PMID: 29378545; PubMed Central PMCID: PMC5789742.
2. van Lier A, Ferreira JA, Mollema L, Sanders EAM, de Melker HE. Intention to vaccinate universally against varicella, rotavirus gastroenteritis, meningococcal B disease and seasonal influenza among parents in the Netherlands: an internet survey. BMC Res Notes. 2017 Dec 4;10(1):672. doi: 10.1186/s13104-017-3004-z. PubMed PMID: 29202798; PubMed Central PMCID: PMC5716237.
3. Pot M, Paulussen TG, Ruiter RA, Eekhout I, de Melker HE, Spoelstra ME, van Keulen HM. Effectiveness of a Web-Based Tailored Intervention With Virtual Assistants Promoting the Acceptability of HPV Vaccination Among Mothers of Invited Girls: Randomized Controlled Trial. J Med Internet Res. 2017 Sep 6;19(9):e312. doi: 10.2196/jmir.7449. PubMed PMID: 28877862; PubMed Central PMCID: PMC5607435.

Burden of disease

1. de Gier B, Mooij S, Hahné SJM. State of Infectious Diseases in the Netherlands, 2017. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2018. RIVM report 2018-0032.
2. McDonald SA, Qendri V, Berkhof J, de Melker HE, Bogaards JA. Disease burden of human papillomavirus infection in the Netherlands, 1989-2014: the gap between females and males is diminishing. Cancer Causes Control. 2017;28(3):203-14.

3. Cassini A, Colzani E, Pini A, Mangen MJ, Plass D, McDonald SA, et al. Impact of infectious diseases on population health using incidence-based disability-adjusted life years (DALYs): results from the Burden of Communicable Diseases in Europe study, European Union and European Economic Area countries, 2009 to 2013. Euro Surveill. 2018;23(16):pii=17-00454.

Adverse events

1. Schurink-Van't Klooster TM, Kemmeren JM, van der Maas NAT, van de Putte EM, Ter Wolbeek M, Nijhof SL, Vanrolleghem AM, van Vliet JA, Sturkenboom M, de Melker HE. No evidence found for an increased risk of long-term fatigue following human papillomavirus vaccination of adolescent girls. Vaccine. 2018 Sep 19. pii:S0264-410X(18)31268-4.
2. Boef AGC, van der Klis FRM, Berbers GAM, Buisman AM, Sanders EAM, Kemmeren JM, et al. Differences by sex in IgG levels following infant and childhood vaccinations: An individual participant data meta-analysis of vaccination studies. Vaccine. 2018;36(3):400-7.

Various research topics addressing evaluation of the NIP in a broader sense

1. Tielemans S, de Melker HE, Hahne SJM, Boef AGC, van der Klis FRM, Sanders EAM, et al. Non-specific effects of measles, mumps, and rubella (MMR) vaccination in high income setting: population based cohort study in the Netherlands. BMJ (Clinical research ed). 2017;358:j3862.
2. van Wijhe M, de Boer P, de Jong H, van Vliet H, Wallinga J, Postma M. Financing vaccination programmes in the Netherlands from a macro-economic perspective: a historical analysis. In preparation. 2018.
3. Hoes J, Boef AGC, Knol MJ, de Melker HE, Mollema L, van der Klis FRM, Rots NY, van Baarle D. Socioeconomic Status Is Associated With Antibody Levels Against Vaccine Preventable Diseases in the Netherlands. Front Public Health. 2018 Jul 27;6:209.
4. van Wijhe M, Tulen AD, Korthals Altes H, McDonald SA, de Melker HE, Postma MJ, Wallinga J. Quantifying the impact of mass vaccination programmes on notified cases in the Netherlands. Epidemiol Infect. 2018 Apr;146(6):716-722.
5. van Wijhe M, McDonald SA, de Melker HE, Postma MJ, Wallinga J. Estimating the Population-Level Effectiveness of Vaccination Programs in the Netherlands. Epidemiology. 2018 Mar;29(2):215-223.

Current NIP

Diphtheria

None

Haemophilus influenzae disease caused by type b (Hib) and other serotypes

1. Monge S, Hahné SJ, de Melker HE, Sanders EA, van der Ende A, Knol MJ. Effectiveness of the DTPa-HBV-IPV/Hib vaccine against invasive *Haemophilus influenzae* type b disease in the Netherlands (2003-16): a case-control study. Lancet Infect Dis. 2018 Jul;18(7):749-757. doi: 10.1016/S1473-3099(18)30166-X. Epub 2018 May 8.

2. Monge S, Mollema L, de Melker H, Sanders E, van der Ende A, Knol M. Clinical Characterization of Invasive Disease Caused by *Haemophilus influenzae* Serotype b in a High Vaccination Coverage Setting. J Pediatric Infect Dis Soc. 2018 Mar 22. doi: 10.1093/jpids/piy020. [Epub ahead of print]

Hepatitis B

1. Cremer J, Hofstraat SHI, van Heiningen F, Veldhuijzen IK, van Benthem BHB, Benschop KSM. Genetic variation of hepatitis B surface antigen among acute and chronic hepatitis B virus infections in The Netherlands. J Med Virol. 2018.
2. Hofstraat SHI, Falla AM, Duffell EF, Hahne SJM, Amato-Gauci AJ, Veldhuijzen IK, et al. Current prevalence of chronic hepatitis B and C virus infection in the general population, blood donors and pregnant women in the EU/EEA: a systematic review. Epidemiol Infect. 2017:1-13.
3. Falla AM, Hofstraat SHI, Duffell E, Hahne SJM, Tavoschi L, Veldhuijzen IK. Hepatitis B/C in the countries of the EU/EEA: a systematic review of the prevalence among at-risk groups. BMC Infect Dis. 2018;18(1):79.

Human papillomavirus (HPV) infection

1. Weele Pvd, Meijer CJ, King AJ. High Whole-Genome Sequence Diversity of Human Papillomavirus Type 18 Isolates. Viruses. 2018;10(2):68.
2. Donken R, King AJ, Bogaards JA, Woestenberg PJ, Meijer C, de Melker HE. High Effectiveness of the Bivalent Human Papillomavirus (HPV) Vaccine Against Incident and Persistent HPV Infections up to 6 Years After Vaccination in Young Dutch Women. The Journal of infectious diseases. 2018;217(10):1579-89.
3. Schurink-Van't Klooster TM, Kemmeren JM, van der Maas NAT, van de Putte EM, Ter Wolbeek M, Nijhof SL, Vanrolleghem AM, van Vliet JA, Sturkenboom M, de Melker HE. No evidence found for an increased risk of long-term fatigue following human papillomavirus vaccination of adolescent girls. Vaccine. 2018 Sep 19. pii:S0264-410X(18)31268-4.
4. Qendri V, Bogaards JA, Berkhof J. Health and Economic Impact of a Tender-Based, Sex-Neutral Human Papillomavirus 16/18 Vaccination Program in the Netherlands. The Journal of infectious diseases. 2017;216(2):210-9.
5. Woestenberg PJ, King AJ, van Benthem BHB, Donken R, Leussink S, van der Klis FRM, et al. Bivalent Vaccine Effectiveness Against Type-Specific HPV Poisitivity: Evidence for Cross-Protection Against Oncogenic Types Among Dutch STI Clinic Visitors. The Journal of Infectious Diseases. 2018:217(2):213-22.
6. Donken R, Tami A, Knol MJ, Lubbers K, van der Sande MAB, Nijman HW, Daemen T, Weijmar Schultz WCM, de Melker HE. Changes in (risk) behavior and HPV knowledge among Dutch girls eligible for HPV vaccination: an observational cohort study. BMC Public Health. 2018 Jul 5;18(1):837. doi: 10.1186/s12889-018-5745-6. PubMed PMID: 29976170; PubMed Central PMCID: PMC6034331.

Measles

1. Klinkenberg D, Hahne SJM, Woudenberg T, Wallinga J. The Reduction of Measles Transmission During School Vacations. Epidemiology. 2018;29(4):562-70.

Meningococcal disease

1. Knol MJ, Ruijs WL, Antonise-Kamp L, de Melker HE, van der Ende A. Implementation of MenACWY vaccination because of ongoing increase in serogroup W invasive meningococcal disease, the Netherlands, 2018. Euro surveillance : 2018;23(16).
2. van Ravenhorst MB, van der Klis FRM, van Rooijen DM, Knol MJ, Stoof SP, Sanders EAM, et al. Meningococcal serogroup C immunogenicity, antibody persistence and memory B-cells induced by the monovalent meningococcal serogroup C versus quadrivalent meningococcal serogroup ACWY conjugate booster vaccine: A randomized controlled trial. Vaccine. 2017;35(36):4745-52.
3. van Ravenhorst MB, van der Klis FRM, van Rooijen DM, Sanders EAM, Berbers GAM. Adolescent meningococcal serogroup A, W and Y immune responses following immunization with quadrivalent meningococcal A, C, W and Y conjugate vaccine: Optimal age for vaccination. Vaccine. 2017;35(36):4753-60.
4. van der Heiden M, van Ravenhorst MB, Bogaard M, Boots AMH, Berbers GAM, Buisman AM. Lower antibody functionality in middle-aged adults compared to adolescents after primary meningococcal vaccination: Role of IgM. Experimental gerontology. 2018;105:101-8.
5. Jonker EFF, van Ravenhorst MB, Berbers GAM, Visser LG. Safety and immunogenicity of fractional dose intradermal injection of two quadrivalent conjugated meningococcal vaccines. Vaccine. 2018;36(26):3727-32.
6. van Ravenhorst MB, den Hartog G, van der Klis FRM, van Rooijen DM, Sanders EAM, Berbers GAM. Induction of salivary antibody levels in Dutch adolescents after immunization with monovalent meningococcal serogroup C or quadrivalent meningococcal serogroup A, C, W and Y conjugate vaccine. PLoS One. 2018 Apr 19;13(4):e0191261.
7. van der Heiden M, Berbers GAM, Fuentes S, van Zelm MC, Boots AMH, Buisman AM. An Explorative Biomarker Study for Vaccine Responsiveness after a Primary Meningococcal Vaccination in Middle-Aged Adults. Front Immunol. 2018 Jan 11;8:1962.
8. Knol MJ, Hahné SJM, Lucidarme J, Campbell H, de Melker HE, Gray SJ, Borrow R, Ladhani SN, Ramsay ME, van der Ende A. Temporal associations between national outbreaks of meningococcal serogroup W and C disease in the Netherlands and England: an observational cohort study. Lancet Public Health. 2017 Oct;2(10):e473-e482.
9. van Lier A, Ferreira JA, Mollema L, Sanders EAM, de Melker HE. Intention to vaccinate universally against varicella, rotavirus gastroenteritis, meningococcal B disease and seasonal influenza among parents in the Netherlands: an internet survey. BMC Res Notes. 2017 Dec 4;10(1):672.
10. van der Heiden M, Duizendstra A, Berbers GAM, Boots AMH, Buisman AM. Tetanus Toxoid carrier protein induced T-helper cell responses upon vaccination of middle-aged adults. Vaccine. 2017 Oct 9;35(42):5581-5588.

Mumps

1. de Wit J, Emmelot ME, Poelen MCM, van Binnendijk RS, van der Lee S, van Baarle D, et al. Mumps infection but not childhood vaccination induces persistent polyfunctional CD8(+) T-cell memory. J Allergy Clin Immunol. 2018;141(5):1908-11 e12.

Pertussis

1. Hovingh ES, Mariman R, Solans L, Hijdra D, Hamstra HJ, Jongerius I, van Gent M, Mooi F, Locht C, Pinelli E. Bordetella pertussis pertactin knock-out strains reveal immunomodulatory properties of this virulence factor. Emerg Microbes Infect. 2018 Mar 21;7(1):39.
2. Hovingh ES, van Gent M, Hamstra HJ, Demkes M, Mooi FR, Pinelli E. Emerging Bordetella pertussis Strains Induce Enhanced Signaling of Human Pattern Recognition Receptors TLR2, NOD2 and Secretion of IL-10 by Dendritic Cells. PloS one. 2017;12(1):e0170027.
3. Hovingh ES, Mariman R, Solans L, Hijdra D, Hamstra HJ, Jongerius I, van Gent M, Mooi F, Locht C, Pinelli E. Bordetella pertussis pertactin knock-out strains reveal immunomodulatory properties of this virulence factor. Emerg Microbes Infect. 2018 Mar 21;7(1):39.
4. Hovingh ES, van den Broek B, Kuipers B, Pinelli E, Rooijakkers SHM, Jongerius I. Acquisition of C1 inhibitor by Bordetella pertussis virulence associated gene 8 results in C2 and C4 consumption away from the bacterial surface. PLoS Pathog. 2017 Jul 24;13(7):e1006531.
5. Hovingh ES. Unraveling the interactions between Bordetella pertussis and the innate immune system. Doctoral thesis, Utrecht University, 3rd May 2018.
6. van der Lee S, Kemmeren JM, de Rond LGH, Öztürk K, Westerhof A, de Melker HE, Sanders EAM, Berbers GAM, van der Maas NAT, Rümke HC, Buisman AM. Elevated Immune Response Among Children 4 Years of Age With Pronounced Local Adverse Events After the Fifth Diphtheria, Tetanus, Acellular Pertussis Vaccination. Pediatr Infect Dis J. 2017 Sep;36(9):e223-e229.

Pneumococcal disease

1. Cremers AJH, Mobegi FM, van der Gaast-de Jongh C, van Weert M, van Opzeeland FJ, Vehkala M, Knol MJ, Bootsma HJ, Välimäki N, Croucher NJ, Meis JF, Bentley S, van Hijum SAFT, Corander J, Zomer AL, Ferwerda G, de Jonge MI. The Contribution of Genetic Variation of Streptococcus Pneumoniae to the Clinical Manifestation of Invasive Pneumococcal Disease. Clin Infect Dis. 2018 May 17.
2. Vissers M, Wijmenga-Monsuur AJ, Knol MJ, Badoux P, van Houten MA, van der Ende A, Sanders EAM, Rots NY. Increased carriage of non-vaccine serotypes with low invasive disease potential four years after switching to the 10-valent pneumococcal conjugate vaccine in The Netherlands. PLoS One. 2018 Mar 30;13(3):e0194823.
3. van Deursen AMM, Schurink-Van't Klooster TM, Man WH, van de Kassteele J, van Gageldonk-Lafeber AB, Bruijning-Verhagen PCJL, de Melker HE, Sanders EAM, Knol MJ. Impact of infant pneumococcal conjugate vaccination on community acquired pneumonia hospitalization in all ages in the Netherlands. Vaccine. 2017 Dec 18;35(51):7107-7113.

4. Wyllie AL, Pannekoek Y, Bovenkerk S, van Engelsdorp Gastelaars J, Ferwerda B, van de Beek D, Sanders EAM, Trzciński K, van der Ende A. Sequencing of the variable region of rpsB to discriminate between Streptococcus pneumoniae and other streptococcal species. Open Biol. 2017 Sep;7(9).
5. Thorrington D, van Rossum L, Knol M, de Melker H, Rümke H, Hak E, van Hoek AJ. Impact and cost-effectiveness of different vaccination strategies to reduce the burden of pneumococcal disease among elderly in the Netherlands. PLoS One. 2018 Feb 9;13(2):e0192640. doi: 10.1371/journal.pone.0192640. eCollection 2018. PubMed PMID: 29425249; PubMed Central PMCID: PMC5806887.

Poliomyelitis

1. Freidl GS, Tostmann A, Curvers M, Ruijs WLM, Smits G, Schepp R, Duizer E, Boland G, de Melker H, van der Klis FRM, Hautvast JLA, Veldhuijzen IK. Immunity against measles, mumps, rubella, varicella, diphtheria, tetanus, polio, hepatitis A and hepatitis B among adult asylum seekers in the Netherlands, 2016.Vaccine. 2018 Mar 14;36(12):1664-1672.

Rubella

1. Freidl GS, Tostmann A, Curvers M, Ruijs WLM, Smits G, Schepp R, et al. Immunity against measles, mumps, rubella, varicella, diphtheria, tetanus, polio, hepatitis A and hepatitis B among adult asylum seekers in the Netherlands, 2016. Vaccine. 2018;36(12):1664-72.

Tetanus

None

Potential NIP target diseases

Hepatitis A

1. Friesema IHM, Sonder GJ, Petrignani MWF, Meiberg AE, Van Rijckevorsel GG, Ruijs WL, et al. Spillover of a hepatitis A outbreak among men who have sex with men (MSM) to the general population, the Netherlands, 2017. Euro Surveill. 2018;23(23):pii=1800265.
2. Mollers M, Boxman ILA, Vennema H, Slegers-Fitz-James IA, Brandwagt D, Friesema IH, et al. Successful Use of Advertisement Pictures to Assist Recall in a Food-Borne Hepatitis A Outbreak in The Netherlands, 2017. Food Environ Virol. 2018.

Respiratory syncytial virus

1. Jans J, Wicht O, Widjaja I, Ahout IM, de Groot R, Guichelaar T, Luytjes W, de Jonge MI, de Haan CA, Ferwerda G. 2017. Characteristics of RSV-Specific Maternal Antibodies in Plasma of Hospitalized, Acute RSV Patients under Three Months of Age. PLoS One 12:e0170877.
2. van Erp EA, van Kasteren PB, Guichelaar T, Ahout IML, de Haan CAM, Luytjes W, Ferwerda G, Wicht O. 2017. In Vitro Enhancement of Respiratory Syncytial Virus Infection by Maternal Antibodies Does Not Explain Disease Severity in Infants. J Virol 91.

Rotavirus

1. Verberk, J.D.M., et al., Biennial Pattern of Rotavirus Gastroenteritis in The Netherlands and a Shifting Age Distribution Following a Low Rotavirus Season, 2010-2016. Pediatr Infect Dis J, 2017.
2. Bruijning-Verhagen P, van Dongen JAP, Verberk JDM, Pijnacker R, van Gaalen RD, Klinkenberg D, de Melker HE, Mangen MJ. Updated cost-effectiveness and risk-benefit analysis of two infant rotavirus vaccination strategies in a high-income, low-endemic setting. BMC Med. 2018 Sep 10;16(1):168. doi: 10.1186/s12916-018-1134-3. PubMed PMID: 30196794; PubMed Central PMCID: PMC6130096.

Varicella zoster virus (VZV) infection

1. Freidl GS, Tostmann A, Curvers M, Ruijs WLM, Smits G, Schepp R, et al. Immunity against measles, mumps, rubella, varicella, diphtheria, tetanus, polio, hepatitis A and hepatitis B among adult asylum seekers in the Netherlands, 2016. Vaccine. 2018;36(12):1664-72.
2. van der Heiden M, de Rond LGH, van Zelm MC, Berbers GAM, Boots AMH, Buisman AM. Age-Dependent Pre-Vaccination Immunity Affects the Immunogenicity of Varicella Zoster Vaccination in Middle-aged Adults. Front Immunol. 2018;9:46.
3. de Boer PT, van Lier A, de Melker H, van Wijck AJM, Wilschut JC, van Hoek AJ, et al. Cost-effectiveness of vaccination of immunocompetent older adults against herpes zoster in the Netherlands: a comparison between the use of adjuvanted subunit vaccine versus live-attenuated vaccine based on a health-economic decision model (submitted for publication).
4. de Boer PT, Pouwels KB, Cox JM, Hak E, Wilschut JC, Postma MJ. Cost-effectiveness of vaccination of the elderly against herpes zoster in The Netherlands. Vaccine. 2013;31(9):1276-83.
5. van Lier A, van Hoek AJ, Opstelten W, Boot HJ, de Melker HE. Assessing the potential effects and cost-effectiveness of programmatic herpes zoster vaccination of elderly in the Netherlands. BMC Health Serv Res. 2010;10:237.
6. van Lier A, Ferreira JA, Mollema L, Sanders EAM, de Melker HE. Intention to vaccinate universally against varicella, rotavirus gastroenteritis, meningococcal B disease and seasonal influenza among parents in the Netherlands: an internet survey. BMC Res Notes. 2017;10(1):672.

Appendix 6 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

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

Cervical cancer screening programme:
https://www.rivm.nl/Onderwerpen/B/Bevolkingsonderzoek_baarmoederhalskanker_voor_professionals

General information for the public

RIVM websites for the public:
https://rijksvaccinatieprogramma.nl/

Available vaccines that are not (yet) part of a public vaccination programme:
www.rivm.nl/vaccinaties

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

Cervical cancer screening programme:
https://www.rivm.nl/Onderwerpen/B/Bevolkingsonderzoek_baarmoederhalskanker

Other NIP-related RIVM reports

Immunisation coverage and annual report National Immunisation Programme in the Netherlands 2017:
https://www.rivm.nl/dsresource?objectid=66a61ddc-2076-43a3-b296-e57265c1b9e6&type=pdf&disposition=inline

Adverse events in the Netherlands Vaccination Programme, reports in 2010 and Review 1994–2010:
http://www.rivm.nl/bibliotheek/rapporten/205051004.pdf

Product information

Product information and package leaflets NIP:
https://rijksvaccinatieprogramma.nl/professionals/productinformatie-vaccinaties

National organisations

General
Ministry of Health, Welfare and Sport:
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):
https://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 (NRLBM):
https://www.amc.nl/web/specialismen/medische-microbiologie/medische-microbiologie/het-nederlands-referentielaboratorium-voor-bacteriele-meningitis.htm

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

The Netherlands Cancer Registry (NKR):
http://www.cijfersoverkanker.nl/

Nederlandse Werkgroep Klinische Virologie (NWKV):
http://www.nvmm.nl/vereniging/commissies-en-werkgroepen/nederlandse-werkgroep-klinische-virologie/

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/infections/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 vaccine schedules
European Centre for Disease Prevention and Control (ECDC):
http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx

World Health Organization (WHO):
http://apps.who.int/immunization_monitoring/globalsummary

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/

National Respiratory and Enteric Virus Surveillance System (NREVSS):
https://www.cdc.gov/surveillance/nrevss/

The Streptococcus pneumoniae Invasive Disease network (SpIDnet):
http://www.epiconcept.fr/produit/spidnet/

WHO Global Polio Laboratory Network (GPLN):
http://www.euro.who.int/en/health-topics/communicable-diseases/poliomyelitis/activities/polio-laboratory-network

Respiratory syncytial virus consortium in Europe (RESCEU):
http://resc-eu.org/

Communication platforms

Epidemic Intelligence Information System (EPIS):
https://ecdc.europa.eu/en/publications-data/epidemic-intelligence-information-system-epis

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/

Annual report Surveillance of influenza and other respiratory infections in the Netherlands:
http://www.rivm.nl/bibliotheek/rapporten/2017-0096.pdf

Tuberculosis

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

Annual report Surveillance of influenza and other respiratory infections in the Netherlands:
http://www.rivm.nl/bibliotheek/rapporten/2017-0096.pdf

National Tuberculosis Control Plan 2016-2020:
http://www.rivm.nl/bibliotheek/rapporten/2016-0028.pdf

Traveller vaccination

Landelijk Coördinatiecentrum Reizigersadvisering:
https://www.lcr.nl/Index.htm

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