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

The *National* Immunisation *Programme* in *the Netherlands*

Surveillance and developments in 2018-2019

The National Immunisation Programme in the Netherlands

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Contents

Synopsis

The National Immunisation Programme in the Netherlands

Surveillance and developments in 2018-2019

In 2018 some 880,000 children aged 0 to 19 were vaccinated under the National Immunisation Programme (NIP). These children received 2,266,000 vaccinations in total. The decline in NIP participation observed since 2014 has ceased.

As in previous years, the number of notified cases in 2018 was low for *Haemophilus influenzae* type b (Hib, 43), meningococcal serogroup C (3), diphtheria (2), tetanus (1), rubella (0), and polio (0). The number of notifications of mumps was slightly higher (73 versus 46 in 2017) and the number of pertussis notifications remained high (4897). In 2018, one infant died of pertussis and early in 2019, one infant and one unvaccinated elderly patient also died due to pertussis. The number of notified measles cases increased to 24 in 2018 and 45 in the first six months of 2019. In June 2019, a local measles outbreak started in Urk, a municipality with a low vaccination coverage. The outbreak is now over.

The number of people with pneumococcal disease caused by a vaccine serotype remained very low (1 child <5 years-old). There is, however, a slight rise in the number of cases of pneumococcal disease caused by serotypes not included in the pneumococcal vaccine. (70 children <5 years-old in winter season 2018/2019 compared to 46 in 2017/2018). Due to an increase in meningococcal serogroup W disease since 2015, MenACWY vaccination has been implemented in 2018. In the first six months of 2019, the number of notified meningococcal serogroup W disease cases decreased (39). A reduction or stabilisation was observed in all age groups except for people 80 years old and over.

The Health Council recommended that an infant's first pertussis-containing vaccination can be postponed and the number of vaccinations reduced from three to two, if a mother is vaccinated against pertussis during pregnancy. Maternal pertussis vaccination will start in December 2019.

In accordance to the recommendation of the Health Council the Ministry of Health decided to introduce HPV vaccination for boys in addition to the programme for girls, to give this vaccination close to the age of nine years. They are also looking into the options for offering unvaccinated boys and girls the vaccination up to 26 years of age.

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 2018-2019

In 2018 zijn ongeveer 880.000 kinderen van 0 tot 19 jaar gevaccineerd via het Rijksvaccinatieprogramma (RVP). In totaal ontvingen zij 2.266.000 vaccinaties. De daling in deelname aan het RVP die sinds 2014 was te zien, is tot stilstand gekomen.

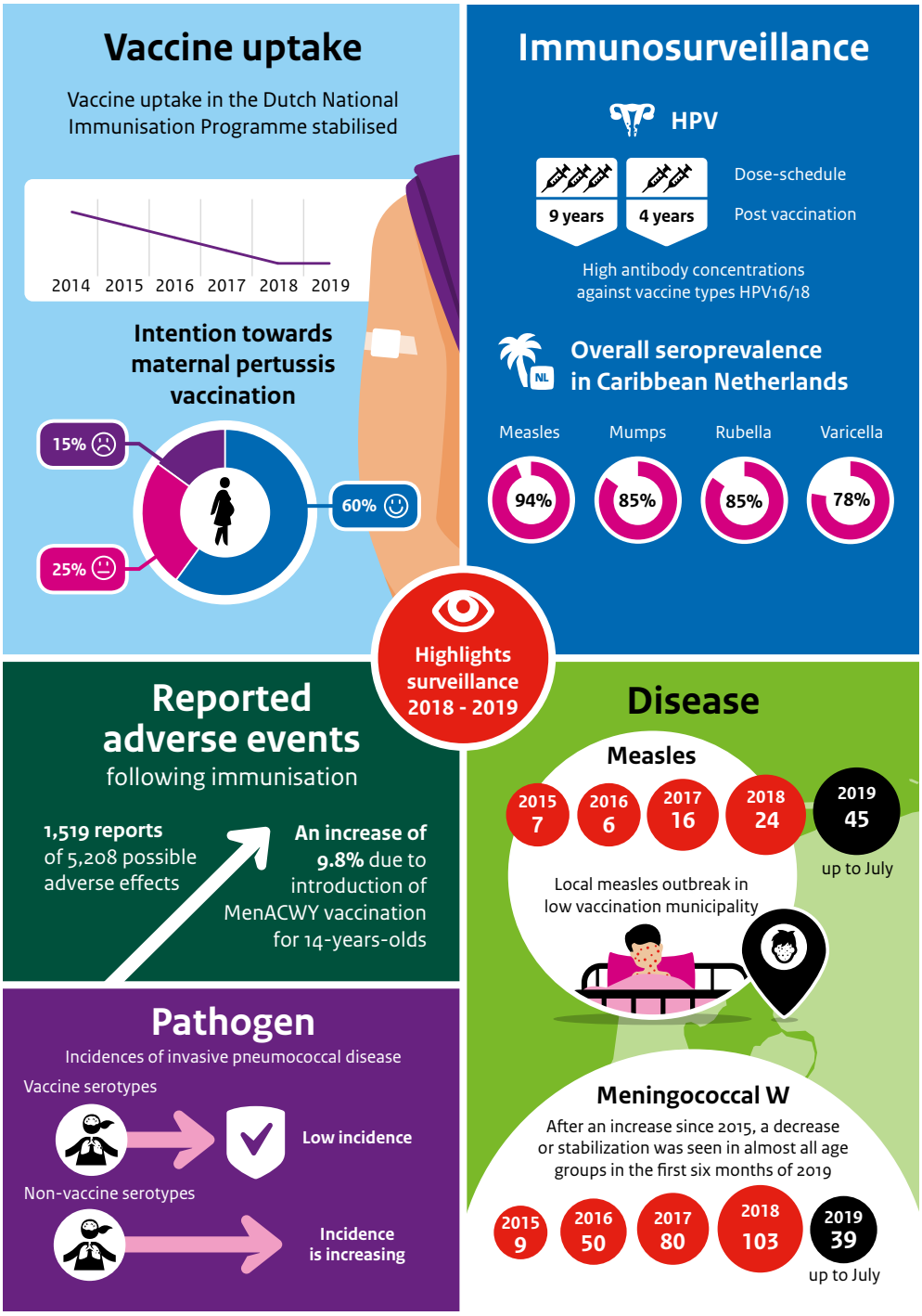
Net als in voorgaande jaren waren er in 2018 weinig meldingen van *Haemophilus influenzae* type b (Hib; 43), meningokokken-C (3), difterie (2), tetanus (1), rodehond (0) en polio (0). Het aantal meldingen van bof was iets hoger (73 versus 46 in 2017); het aantal meldingen van kinkhoest bleef onverminderd hoog (4897). In 2018 overleed een jonge zuigeling aan kinkhoest, en begin 2019 een zuigeling en een ongevaccineerde oudere patiënt. Het aantal gevallen van mazelen nam toe van 24 in 2018 tot 45 in de eerste helft van 2019. In juni 2019 begon een lokale uitbraak van mazelen in Urk, een gemeente met relatief weinig gevaccineerde mensen. De uitbraak is inmiddels voorbij.

Het aantal mensen met pneumokokkenziekte door een serotype dat in het vaccin zit bleef erg laag (1 kind jonger dan 5 jaar). Wel hebben wat meer mensen pneumokokkenziekte gekregen door serotypes die niet in het vaccin zitten (70 kinderen jonger dan 5 jaar in winterseizoen 2018/2019 ten opzichte van 46 in 2017/2018). Door een stijging van het aantal gemelde meningokokkenziekte type W sinds 2015 is in 2018 de MenACWY-vaccinatie ingevoerd. In de eerste zes maanden van 2019 daalde het aantal meldingen van meningokokkenziekte type W (39). Alleen bij mensen die ouder zijn dan 80 was deze daling niet te zien.

De Gezondheidsraad heeft geadviseerd dat de eerste vaccinatie van een baby kan worden uitgesteld wanneer de moeder tegen kinkhoest is gevaccineerd tijdens de zwangerschap. Het aantal vaccinaties voor de baby kan hierdoor worden teruggebracht van drie naar twee. De vaccinatie voor zwangeren start in december 2019.

Het ministerie van VWS heeft op advies van de Gezondheidsraad besloten om de HPV-vaccinatie ook voor jongens aan te bieden en de leeftijd van vaccinatie te verlagen van 12 naar 9 jaar. Ook wordt gekeken naar de mogelijkheden om ongevaccineerde jongens en meisjes de vaccinatie tot en met 26 jaar nog aan te bieden.

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


Vaccine uptake
Vaccine uptake in the Dutch National Immunisation Programme stabilised
2014 2015 2016 2017 2018 2019
Intention towards maternal pertussis vaccination
15%
60%
25%
Immunosurveillance
HPV
9 years
4 years
Dose-schedule
Post vaccination
High antibody concentrations against vaccine types HPV16/18
Overall seroprevalence in Caribbean Netherlands
Measles
Mumps
Rubella
Varicella
94%
85%
85%
78%
Highlights surveillance 2018 - 2019
Reported adverse events
following immunisation
1,519 reports of 5,208 possible adverse effects
An increase of 9.8% due to introduction of MenACWY vaccination for 14-years-olds
Pathogen
Incidences of invasive pneumococcal disease
Vaccine serotypes
Low incidence
Non-vaccine serotypes
Incidence is increasing
Disease
Measles
2015 7
2016 6
2017 16
2018 24
2019 45
up to July
Local measles outbreak in low vaccination municipality
Meningococcal W
After an increase since 2015, a decrease or stabilization was seen in almost all age groups in the first six months of 2019
2015 9
2016 50
2017 80
2018 103
2019 39
up to July

Meningococcal B disease

Vaccination not recommended

Reassess after 3 years

Uncertainty on the effectiveness

No herd protection

Life threatening disease and possible residual effects

High fever

Unfavorable cost-effectiveness

Meningococcal ACWY disease

=

14 months

Continue with vaccination

+

14 years

Implement vaccination in the National Immunistion Programme

Decisions Ministry of Health

HPV

Recommended to vaccinate

Girls close to nine years of age

Boys in addition to girls

12

9

9

Offer supplemental vaccination to unvaccinated adults up to 26

26

Herpes Zoster

Recommended

Vaccination of elderly people with the new herpes zoster vaccine

According to the Health Council the **new herpes zoster vaccine** cost-effectiveness should not exceed the commonly used reference value of € 20,000 per QALY

Preface

This report presents an overview of surveillance and developments 2018 and the first part of 2019 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, respiratory syncytial virus (RSV), rotavirus, 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 is structured as follows:
Chapter 1 contains a summary introduction of the NIP organisation, new recommendations from the Health Council of the Netherlands, and new decisions issued by the Ministry of Health, Welfare and Sports. Recent data regarding vaccination coverage are discussed in Chapter 2. Chapter 3 focuses on the burden of diseases included in the NIP. Public acceptance of vaccination and NIP communication are described in Chapter 4, whilst information on adverse events following immunisation (AEFI) is given in Chapter 5. Chapter 6 presents various research topics that address the evaluation of the NIP in a broader sense. Chapter 7 focuses on current NIP target diseases. For each disease, the section starts with key points outlining the most prominent findings followed by figures and tables. An update of information on epidemiology, the pathogen, the outcome of current and ongoing studies, and international developments is then provided. Vaccination coverage and developments in the current NIP target diseases in the Dutch overseas territories, including the Dutch Caribbean islands, are presented in Chapter 8. Chapter 9 describes potential new target diseases that are under consideration for (future) vaccination. Finally, Chapter 10 provides an overview of vaccines for infectious diseases that are undergoing clinical trials and are potentially relevant for the Netherlands.

Appendix 1 describes the surveillance methods used to monitor the NIP. Appendix 2 reports on mortality and morbidity figures from 1997 onwards based on various data sources. Appendix 3 contains an overview of changes in the NIP since 2000, whilst 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 against 12 vaccine-preventable diseases (VPDs), i.e. diphtheria, pertussis, tetanus, poliomyelitis, *Haemophilus influenzae* disease, measles, mumps, rubella, meningococcal disease, hepatitis B, pneumococcal disease, and human papillomavirus (HPV) infection (girls) (Figure 1). This report presents surveillance data and scientific developments relevant for the Netherlands 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

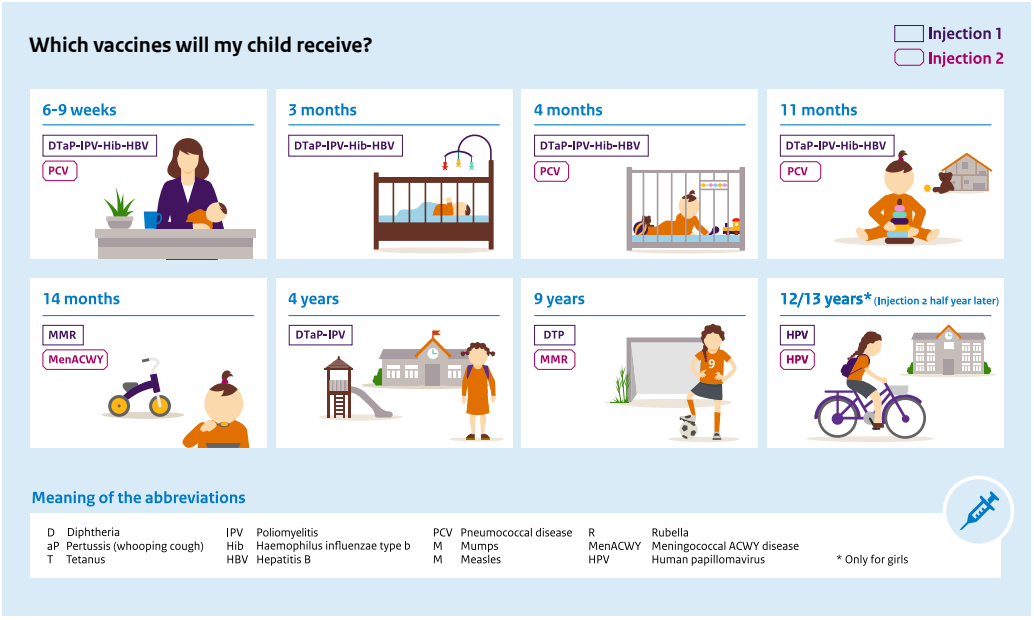
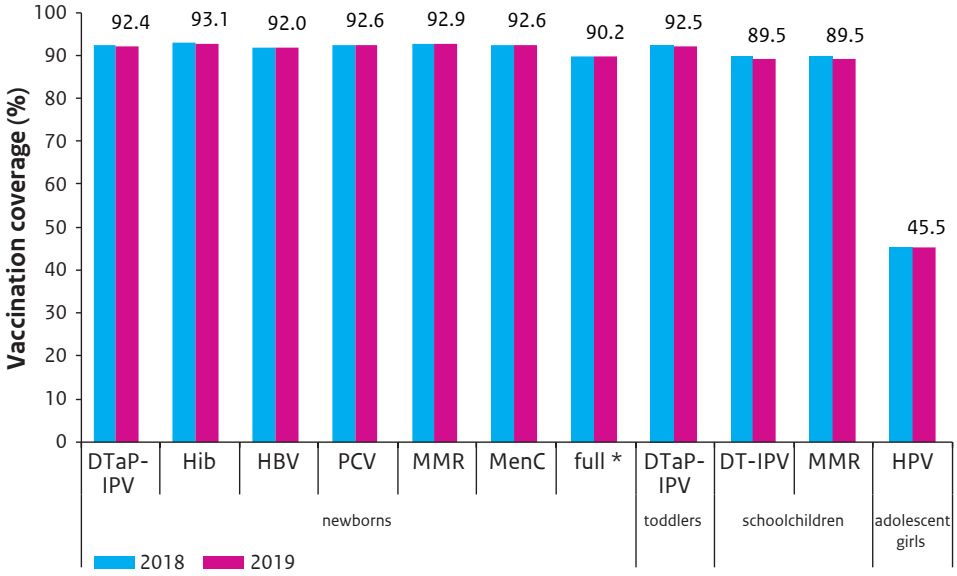


Figure 1 NIP vaccination schedule
Source: *http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals*

Vaccination coverage

The decline in vaccination coverage has ceased; coverage for most vaccinations has remained roughly the same as in the previous year. Provisional figures for younger children show a slight increase. For HPV, even almost 65% of girls born in 2006 received a first HPV vaccination compared with 44%-47% for girls born in the period 2003-2005.



* 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 2018 and 2019
Source: Præventis

Acceptance of vaccination

A RIVM study conducted at the end of 2018 and beginning of 2019 showed that approximately 70% of pregnant women have already heard of the maternal pertussis vaccination (MPV). About 60% had a positive intention to receive the MPV, 25% were neutral, and 15% had a low intention. With regard to HPV vaccination, a more in-depth study on the effectiveness of the tool developed to help mothers reach a decision about HPV vaccination for their daughters showed that the extent to which mothers completed this intervention had a positive impact on their daughters' vaccination uptake. With regard to communication, vaccination information will now also be provided for younger high school students.

Burden of disease

For the year 2018, the estimated burden of disease caused by (partially) vaccine-preventable diseases, as expressed in Disability Adjusted Life Years (DALYs), was highest for HPV (based on the burden in 2017 instead of 2018: 18,000 DALYs (75% among women)), invasive pneumococcal disease (10,800 DALYs/year), pertussis (2,000 DALYs/year), rotavirus infection (1,200 DALYs/year), invasive meningococcal disease (1,100 DALYs/year), and invasive *Haemophilus influenzae* disease (1,000 DALYs/year). For most diseases, the estimated burden in 2018 was comparable to the estimated burden in 2017. The burden for hepatitis A was lower in 2018 than in the outbreak year 2017.

Adverse events

In 2018, Lareb received 1,519 notifications representing a total of 5,208 adverse events following immunisation (AEFI). Compared to 2017, the number of reports increased by 9.8%, while the number of notified AEFIs decreased by 4.0%. The increase in the number of notifications can be ascribed to the introduction of the MenACWY vaccination in adolescents. No new signals of disturbing adverse events were found.

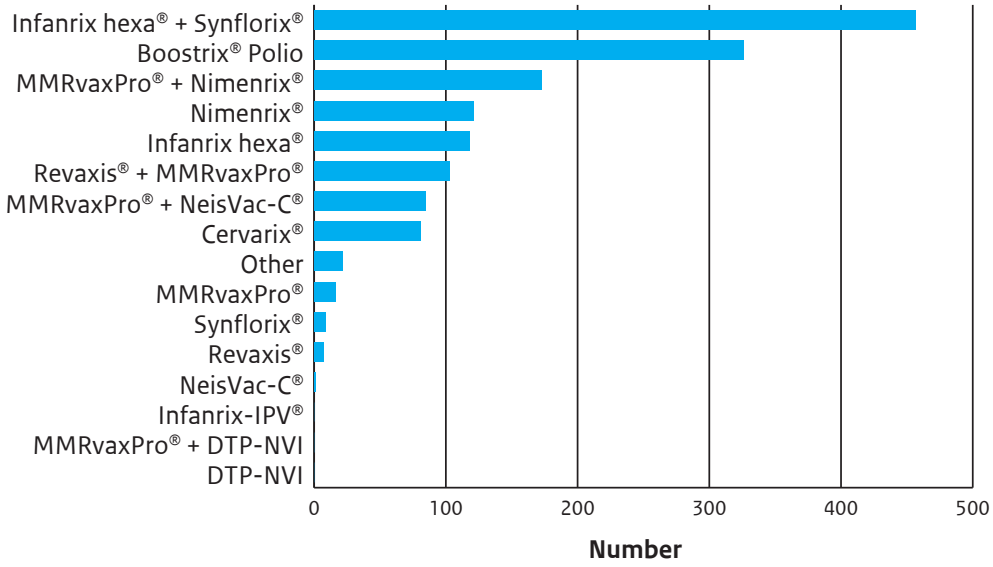


Figure 3 Number of reports of adverse events per suspected vaccine(s) in 2018
Source: Lareb

NIP-wide research topics

After infant and childhood vaccinations, differences in IgG between boys and girls were generally small and inconsistent, either between pathogens or within pathogens. If differences were observed, girls were favoured over boys.

Current NIP

Diphtheria

In 2018, two notifications of diphtheria were received. Both cases were older than 30 years of age and vaccinated with three or more injections.
Three countries in the Region of the Americas (Colombia, Haiti and the Bolivarian Republic of Venezuela) reported confirmed diphtheria cases in 2018. The two cases in the Netherlands were not related to these outbreaks. In 2019 Haiti and Venezuela continue to report confirmed cases, which poses a potential threat for the Dutch Leeward Antilles due to the close proximity of Venezuela and the influx of refugees. In Yemen and Bangladesh, probable diphtheria has been reported in 2018 and 2019 due to the humanitarian crisis and low vaccination coverage in the governorates and refugee camps.

Haemophilus influenzae disease

In 2018, the number of cases of *Haemophilus influenzae* type b (Hib) disease was similar to 2017 (43 vs. 46 cases). In 2018, the incidence of Hib disease was highest among children <5 years old (2.1 per 100,000). The rising trend in incidence observed from 2011 to 2016 ceased in 2017 and 2018.
There were 11 vaccinated Hib cases (55% of vaccine eligible Hib cases) in 2018, resulting in a Hib vaccine effectiveness estimate of 91%, similar to previous years.

Hepatitis B

Of the total number of 1,153 notified hepatitis B cases, 9% had an acute infection and 89% a chronic infection.
The incidence of acute hepatitis B reports (n=104) remained stable at 0.6 per 100,000 population in 2018. Among both men and women, heterosexual contact was the most frequently reported risk factor for acute HBV infection. No cases of acute hepatitis B were reported among children born after the introduction of universal HBV vaccination in 2011.
In 2018, genotype A continued to be the dominant genotype among acute HBV cases with 63% of 63 genotyped cases, followed by genotype D (16%).
After an increase in 2017, the number of newly diagnosed chronic HBV infections dropped to 1,030 in 2018, corresponding to an incidence of 6.5 per 100,000. Ninety percent of all individuals with a chronic HBV infection were born abroad. In contrast, 79% of all individuals with an acute HBV infection were born in the Netherlands.

Human papillomavirus (HPV) infection

The incidence of cervical cancer in 2018 increased to 9.14 per 100,000 (n=832) while the number of deaths caused by cervical cancer has remained relatively stable (n=217). The incidence of other HPV-related cancers was stable as well. In a prospective cohort study (HAVANA), high vaccine effectiveness (VE) against vaccine types HPV16/18 was found for persistent cervicovaginal infections up to eight years post vaccination. In addition, a study among young STI clinic visitors (PASSYON study) showed comparable high VE against anal HPV 16/18 infections. Regarding immunogenicity, high antibody concentrations were observed against vaccine types HPV16/18 following the three-, two-, and one-dose schedule at nine, four, and seven years post vaccination, respectively.

In accordance with the advice of the Health Council of the Netherlands (June 2019) the Ministry decided to introduce male vaccination, to lower the age of routine vaccination for both girls and boys to around nine years. They are also looking into the options for offering unvaccinated boys and girls the vaccination up to 26 years of age.

Measles

The number of measles cases is on the rise, with 24 notified cases in 2018 and 45 in the first six months of 2019. A local outbreak in a low vaccination municipality started in June 2019, with 11 patients reported in that month. Ten out of these 69 patients were too young to be vaccinated. Genotypes B3 and D8 were detected. These are the two genotypes that are also detected most frequently in other European countries.

Meningococcal disease

The number of notified cases with meningococcal serogroup C disease is still very low, with only three cases reported in 2018. Since 2015, the number of cases with meningococcal serogroup W (MenW) disease has been rising, with 103 cases (0.60 per 100,000 population) and 23 deaths reported in 2018. In the first six months of 2019, the incidence of MenW decreased to 0.45 per 100,000 population (n=39). A decrease or stabilisation of incidence was observed in all age groups except among 80-year-olds and over. Since May 2018, MenACWY vaccination at 14 months of age is included in the NIP. Between October 2018 and June 2019, all children born in 2001-2005 were offered MenACWY vaccination (preliminary uptake 84%). There have been no MenW cases, either vaccinated or unvaccinated, in the cohorts eligible for MenACWY vaccination since its implementation. Whether the decrease or stabilisation of incidence in other age groups is due to implementation of MenACWY vaccination is difficult to say.

The incidence of meningococcal serogroup B (MenB) disease has been declining steadily since the late nineties, having stabilised at 0.5 per 100,000 since 2011. The incidence of MenB disease was highest in children under 5 years of age, with 31 cases in 2018 (3.6 per 100,000). The Health Council did not recommend adding MenB vaccination to the NIP due to uncertainty with regard to the effectiveness of the vaccine, the risk of fever after vaccination, and unfavourable cost-effectiveness. The council proposed a review of its recommendation when new data becomes available.

Mumps
The incidence of mumps in 2018 was low with 73 notified cases (0.4 per 100,000 population) but higher compared to the year before. Most of the mumps cases in the Netherlands were caused by mumps virus genotype G.

Pertussis
The 2018 pertussis incidence was comparable to 2017, with an incidence of 28.5 per 100,000 population (4,897 cases) compared with 28.7 in 2017 (4,912 cases). The IR remained highest for the 0- to 5-month-olds. (IR 156.9/100,000; 133 cases) One infant died from pertussis in 2018. In the first trimester of 2019, a rise in pertussis cases was observed in all age groups (2.236 cases up to April; IR of 38.8), which fits the long-term epidemiological pattern of pertussis. The increase was most prominent in the age group 0- to 5-months (IR of 192.3 versus 156.9 in 2018) and 10-19 years (IR of 91.3 versus 62.5 in 2018). One infant and one unvaccinated patient above 80 years of age died of pertussis in the beginning of 2019. In 2018, the prevalence of pertactin-deficient strains was 24% as compared with 9.7% in 2017. This sharp increase seems to continue as 42% of all strains collected in 2019 lack this vaccine antigen. The number of pregnant women who get themselves actively vaccinated against pertussis is rising, with an estimated vaccination coverage of 13% in 2018 and 26% up to 1 April 2019. The implementation of maternal pertussis vaccination in the context of the NIP is expected to start in December 2019.

Pneumococcal disease
In children <5 years of age, introduction of pneumococcal conjugate vaccination (PCV) in 2006 led to a 59% reduction of invasive pneumococcal disease (IPD) in season 2018/19. In 2018/19, 71 children <5 years of age with IPD were reported. Since 2013/14, however, the IPD incidence in children <5 years of age has been rising slightly because of a slow increase of IPD caused by serotypes not included in the 10-valent PCV. In other age groups, similar trends were observed with very low incidence of IPD caused by vaccine serotypes and increasing incidence of IPD due to non-vaccine serotypes, compromising the overall impact of PCV implementation.
From 2020, the 23-valent pneumococcal polysaccharide vaccine (PPV23) will be offered to all 60-, 65-, 70- and 75-year-olds in the Netherlands by their general practitioner.

Poliomyelitis
In 2018 and 2019 up to 1 July, no cases of poliomyelitis were notified. Poliovirus was not detected in the Netherlands.
In Nigeria, one of the three countries with endemic polio, no WPV cases were reported in 2018 and 2019 up to 10 July. In Afghanistan and Pakistan, 33 WPV1 cases were reported in 2018 and 42 WPV1 cases in 2019 up to 10 July. Outbreaks of circulating vaccine-derived poliovirus in non-endemic countries threaten the eradication of the virus.

Rubella
In 2018, no rubella cases were notified. The number of rubella cases continued to decline across Europe in 2018.

Tetanus

One tetanus case was reported in 2018. It concerned a man who was born before introduction of the NIP. According to LCI guidelines he should have been immunised with Tetanus Toxoid and anti-Tetanus Immunoglobulins as post-exposure prophylaxis. However, he only received Tetanus Toxoid.

The immunisation programme in the Caribbean Netherlands

In general, vaccination coverage in the Dutch overseas territories, including the Caribbean Netherlands (Bonaire, St. Eustatius and Saba) is high. In 2018, no NIP-diseases were reported on Bonaire, Saba and St. Eustatius.

Data from the Health Study Caribbean Netherlands revealed that protection in the Caribbean Netherlands, overall seroprevalence for measles was relatively high (94%), but lower for mumps and rubella (both 85%). Outbreaks of measles and diphtheria, which started in Venezuela due to a humanitarian crisis, remain ongoing in the WHO Region of the Americas. Hence, healthcare workers in the Dutch overseas territories should be alert so as to detect cases and adequately prevent transmission if needed. Varicella seroprevalence in the Caribbean Netherlands (overall 78%) increases steadily with age; however, unlike in the Netherlands, it increases more slowly and does not reach 100% in the elderly. This results in a population susceptible to varicella at an older age, including pregnant women and elderly, with the potential of developing more severe disease and sequelae.

As of 1 January 2019, the age of administration of the booster MMR- vaccine on Bonaire was lowered from 9 years to 18 months in order to ensure timely protection of children.

Potential NIP target diseases

Hepatitis A

In 2018, 188 hepatitis A cases were reported, half the number of cases reported in 2017 (n=374) although higher compared to 2011-2016 (80-125 cases). The large-scale international outbreak of hepatitis A among MSM peaked in 2017. However, cases related to this outbreak were still seen in 2018. About three-quarters of the cases reported in 2018 were 20 years or over. Thirty-six per cent of all Dutch cases were reported to be travel-related, with Morocco reported most frequently.

Respiratory syncytial virus (RSV) infection

In the 2018/2019 respiratory season, RSV was reported in 12% of all ILI- and ARI samples compared to 6% in 2017/2018 and 12% in 2016/2017. A phase 3 trial of a maternal RSV vaccine showed no significant impact on the primary study endpoint, i.e. medically relevant RSV-related lower respiratory tract infections but the effectiveness against infant RSV hospitalisations was estimated at 44.4% (95%CI 19.6-61.5%) and against RSV disease with severe hypoxemia 48.3% (95%CI -8.2 - +75.3). A phase 2 trial of a long-lived monoclonal antibody showed a 70.1% risk reduction in medically relevant RSV-related lower respiratory tract infections.

Rotavirus infection

In 2018, 1,129 detected cases of rotavirus were reported, slightly more than in 2017 (n=1,047). After the exceptionally low rotavirus seasons in 2014 (n=607 detections) and 2016 (n=679 detections), the rotavirus seasons of 2017 and 2018 were comparable, contradicting the previous hypothesis of a shift in the rotavirus season to a biennial pattern. Until mid-July 2019, slightly fewer rotavirus cases have been observed compared with the same period in 2018 (2018: n=1033; 2019: n=911). Half of the samples typed in 2018 corresponded to rotavirus serotype G9 (89/179). The most frequently detected genotypes were G9P8 (60/179) and G3P8 (56/179). In July 2018, the Ministry of Health, Welfare and Sport decided to offer rotavirus vaccination to high-risk infants as part of the NIP. The implementation process is ongoing.

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

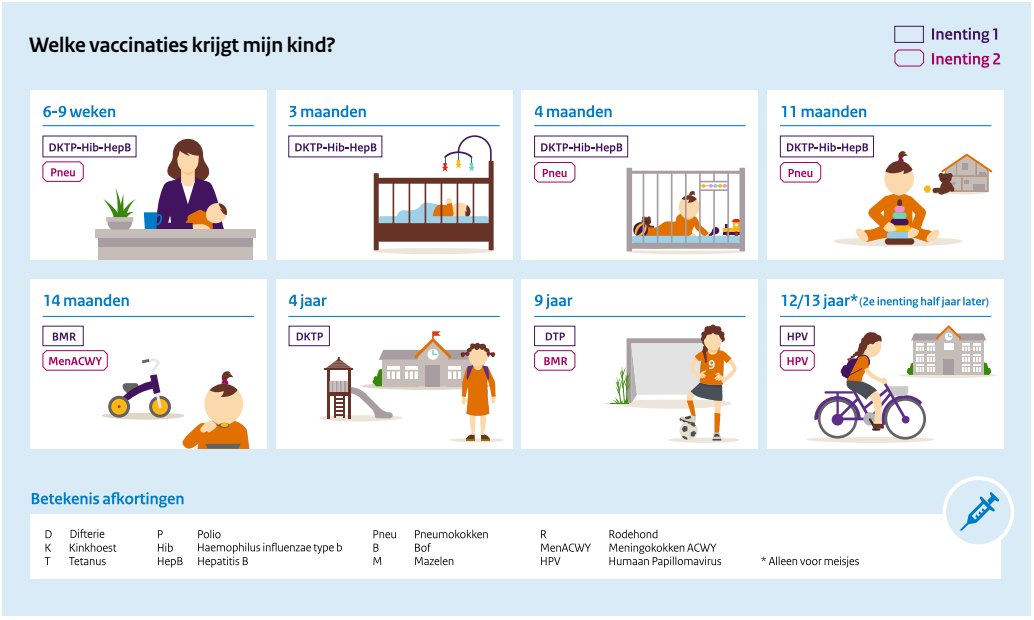
The VZV epidemiology (incidence of GP consultations, hospitalisations and deaths) in the Netherlands has not changed in recent years and is comparable to that of previous years; in 2017, GPs recorded about 48,000 varicella and 90,000 herpes zoster episodes (280 and 530 episodes per 100,000 population respectively).

In July 2019, the Health Council issued a positive recommendation with regard to vaccinating the elderly against herpes zoster with the new Shingrix® vaccine. However, according to the Health Council, the cost-effectiveness of vaccination should not exceed the commonly used reference value of €20,000 per QALY, which is not the case at the current 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).

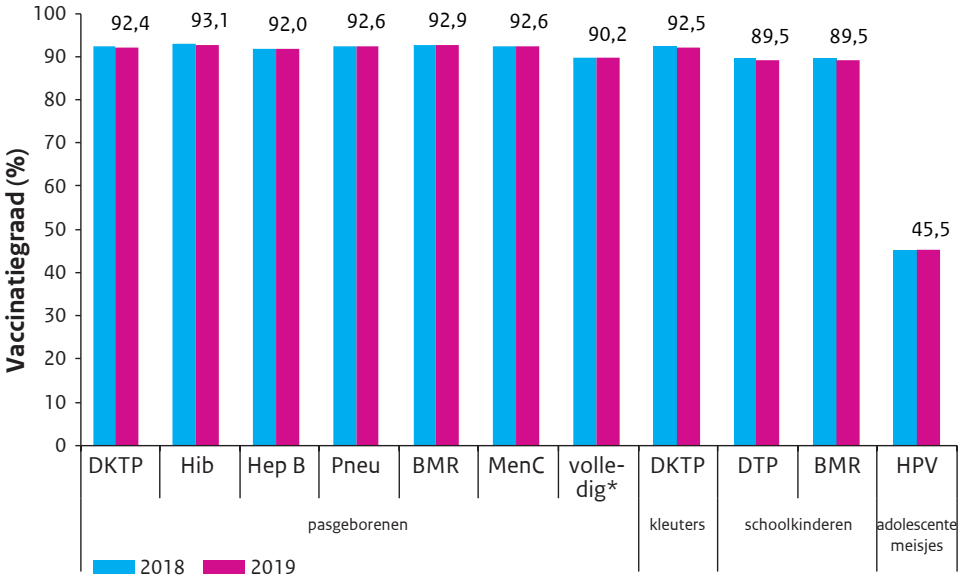
Huidig vaccinatieschema



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

Vaccinatiegraad

Er is een einde gekomen aan de daling van de vaccinatiegraad; voor de meeste vaccinaties is deze ongeveer hetzelfde gebleven als in het voorgaande jaar. Voorlopige cijfers voor jongere kinderen laten een kleine toename zien. Voor HPV heeft zelfs bijna 65% van de meisjes geboren in 2006 een eerste HPV-vaccinatie gekregen, vergeleken met 44%-47% voor meisjes geboren in de periode 2003-2005.



* 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 en 2019
Bron: Præventis

Acceptatie van vaccinatie

Een studie uitgevoerd door het RIVM eind 2018/begin 2019 liet zien dat ongeveer 70% van de zwangere vrouwen al over maternale kinkhoest vaccinatie (MKV) had gehoord voorafgaand aan de invoering. Ongeveer 60% van de zwangere vrouwen had een positieve vaccinatiebereidheid voor MKV, 25% was neutraal en 15% was negatief. In deze studie had 45% van de zwangere vrouwen die al ver genoeg waren in de zwangerschap het vaccin al gehaald. Onderzoek naar het effect van de keuzehulp om ouders te ondersteunen bij het maken van een beslissing om hun dochter te vaccineren tegen HPV, liet zien dat moeders die meer van de keuzetool hadden gelezen hun dochter vaker hebben laten vaccineren. Er is een biologieles ontwikkeld over vaccinatie voor jongere middelbare scholieren.

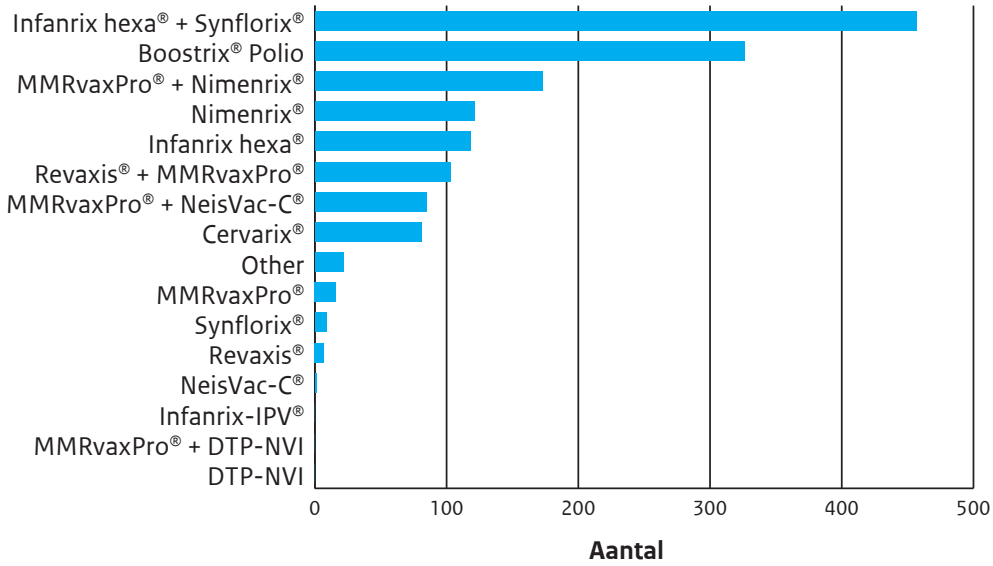
Ziektelast

De geschatte ziektelast veroorzaakt door ziekten die (deels) door vaccinatie te voorkomen zijn, uitgedrukt in Disability Adjusted Life Years (DALYs), was in 2018 het hoogst voor HPV (gebaseerd op de ziektelast in 2017 in plaats van 2018: 18.000 DALYs (75% voor vrouwen)), invasieve pneumokokkenziekte (10.800 DALYs per jaar), kinkhoest (2.000 DALYs per jaar), rotavirusinfectie (1.200 DALYs per jaar), invasieve meningokokkenziekte (1.100 DALYs per jaar)

en invasieve ziekte veroorzaakt door *Haemophilus influenzae* (1.000 DALYs per jaar). Voor de meeste ziekten was de geschatte ziektelast in 2018 vergelijkbaar met de geschatte ziektelast in 2017. Voor hepatitis A was de ziektelast in 2018 lager dan in het uitbraakjaar 2017.

Bijwerkingen

In 2018 ontving Bijwerkingencentrum Lareb 1.519 meldingen van in totaal 5.208 mogelijke bijwerkingen van vaccins. In vergelijking met 2017 is het aantal meldingen gestegen met 9.8%. Dit wordt hoofdzakelijk veroorzaakt door de introductie van de meningokokken ACWY vaccinatie bij 14-jarigen. Het aantal geregistreerde mogelijke bijwerkingen na vaccinatie per melding is gedaald met 4.0%.
Er werden geen nieuwe signalen van verontrustende bijwerkingen gevonden.



Figuur 3 Aantal meldingen van mogelijke bijwerkingen per vaccin(s) in 2018
Bron: Lareb

RVP-brede onderzoeksthema's

Na vaccinaties bij zuigelingen en kinderen waren de IgG-verschillen tussen jongens en meisjes over het algemeen klein en niet consistent, noch tussen pathogenen noch binnen pathogenen. Als er verschillen werden geconstateerd, waren IgG-levels in meisjes hoger dan in jongens.

Huidig RVP

Difterie

In 2018 zijn er twee patiënten van ouder dan 30 jaar gemeld met difterie. Beide personen waren gevaccineerd.
In Zuid- en Midden-Amerika zijn in Haïti en Venezuela uitbraken van difterie gaande door een lage vaccinatiegraad. De uitbraak in Venezuela kan door de nabijheid en de stroom vluchtelingen een risico vormen voor de Nederlandse Antillen. Ook in Yemen en Bangladesh wordt gekampt met difterie-uitbraken door de lage vaccinatiegraad en de humanitaire crisis die daar gaande is. De twee Nederlandse meldingen waren niet gerelateerd aan deze uitbraken.

Haemophilus influenzae-ziekte

In 2018 was het aantal gevallen van invasieve ziekte veroorzaakt door *Haemophilus influenzae* type b vergelijkbaar met 2017 (43 versus 46). De hoogste incidentie werd gevonden onder kinderen jonger dan vijf jaar (2,1 per 100.000). De toename die zichtbaar was van 2011 tot 2016, werd niet voortgezet in 2017 en 2018. Er waren 11 gevaccineerde Hib-gevallen in 2018 (55% van alle Hib-gevallen die in aanmerking kwamen voor vaccinatie), wat resulteerde in een schatting van de vaccineffectiviteit (91%) die vergelijkbaar is met voorgaande jaren.

Hepatitis B

Van de in totaal 1.153 gemelde gevallen van hepatitis B had 9% een acute infectie en 89% een chronische infectie.
De incidentie van acute hepatitis B-meldingen (n=104) bleef stabiel in 2018 op 0,6 per 100.000 inwoners. Bij zowel mannen als vrouwen was heteroseksueel contact de meest gemelde risicofactor voor een acute HBV-infectie. Er werden geen gevallen gemeld van acute hepatitis B onder kinderen geboren na de introductie van universele HBV vaccinatie in 2011. In 2018 bleef genotype A het dominante genotype onder acute HBV-gevallen met 63% van de 63 getypeerde gevallen, gevolgd door genotype D (16%).
Na een toename in 2017 daalde het aantal nieuw gediagnosticeerde chronische HBV-infecties tot 1.030 in 2018, dat overeenkomt met een incidentie van 6,5 per 100.000 inwoners. Negentig procent van de mensen met een chronische HBV-infectie werd in het buitenland geboren. Daarentegen is 79% van de mensen met een acute HBV-infectie in Nederland geboren.

Humaan papillomavirus (HPV)-infectie

De incidentie van baarmoederhalskanker is in 2018 toegenomen tot 9,14 per 100.000 (n=832) terwijl het aantal doden veroorzaakt door baarmoederhalskanker stabiel is gebleven (n=217). De incidentie van andere HPV-gerelateerde kankers was tevens stabiel. In een prospectieve cohortstudie (HAVANA) werd een hoge vaccineffectiviteit (VE) gevonden tegen aanhoudende vaginale HPV-infecties tot in ieder geval 8 jaar na de vaccinatie. Daarnaast werd in een studie onder jonge SOA polibezoekers (PASSYON studie) een vergelijkbare hoge VE gevonden tegen anale HPV-infecties. Met betrekking tot immunogeniciteit werden hoge antistofconcentraties gevonden tegen de vaccintypen HPV16/18. Dit was het geval bij meisjes die drie, twee en één

doses van het vaccin hadden ontvangen zoals gemeten tot respectievelijk negen, vier en zeven jaar na vaccinatie.
Het ministerie van Volksgezondheid, Welzijn en Sport besloot op advies van de Gezondheidsraad om naast meisjes ook jongens tegen HPV te gaan vaccineren en om het vaccin aan te gaan bieden op negenjarige leeftijd in plaats van 12/13 jaar. Daarnaast wordt gekeken naar de mogelijkheden om ongevaccineerde jongens en meisjes de vaccinatie tot en met 26 jaar nog aan te bieden.

Mazelen
Het aantal gevallen van mazelen neemt toe van 24 gemelde gevallen in 2018 tot 45 in de eerste zes maanden van 2019. Een lokale uitbraak in een gemeente met een lage vaccinatiegraad begon in juni 2019 waarbij 11 patiënten werden gemeld in die maand. Tien van deze 69 patiënten waren te jong voor vaccinatie. Genotypen B3 en D8 werden gedetecteerd, dit zijn de twee genotypen die ook in andere Europese landen het meest worden gedetecteerd.

Meningokokkenziekte
Het aantal gevallen met meningokokken serogroep C is nog steeds erg laag, met slechts drie gemelde gevallen in 2018. Sinds 2015 is het aantal gevallen met meningokokken serogroep W (MenW) toegenomen met in 2018 103 gevallen (0,60 per 100.000) en 23 sterfgevallen gemeld. In de eerste zes maanden van 2019 daalde de incidentie van MenW tot 0,45 per 100.000 (n=39). Een afname of stabilisatie van de incidentie werd waargenomen in alle leeftijds-groepen, behalve >=80-jarigen. Sinds mei 2018 maakt MenACWY-vaccinatie bij 14 maanden deel uit van het RVP. Tussen oktober 2018 en juni 2019 is aan alle kinderen die in 2001-2005 zijn geboren, MenACWY-vaccinatie aangeboden (voorlopige vaccinatiegraad 84%). Sinds de implementatie zijn er geen gevallen van MenW, gevaccineerd of niet-gevaccineerd, in de cohorten die in aanmerking komen voor MenACWY-vaccinatie. Of de daling of stabilisatie van de incidentie bij andere leeftijdsgroepen het gevolg is van de uitvoering van MenACWY-vaccinatie, is moeilijk te zeggen.
De incidentie van meningokokken serogroep B (MenB) is sinds de late jaren negentig gestaag afgenomen en is sinds 2011 gestabiliseerd op een incidentie van 0,5 per 100.000. De incidentie van de ziekte van MenB was het hoogst bij kinderen jonger dan 5 jaar met 31 gevallen in 2018 (3,6 per 100.000). De Gezondheidsraad heeft niet aanbevolen om MenB-vaccinatie toe te voegen aan het RVP vanwege onzekerheid over de effectiviteit van het vaccin, de kans op koorts na vaccinatie en ongunstige kosteneffectiviteit. De Gezondheidsraad heeft geadviseerd dit advies te heroverwegen wanneer nieuwe gegevens beschikbaar komen.

Bof
De incidentie van bof in 2018 was laag (0,4 per 100.000; n=73) maar hoger dan het voorgaande jaar. De meeste bofgevallen in Nederland werden veroorzaakt door het bofvirus genotype G.

Kinkhoest

De incidentie van kinkhoest was in 2018 vergelijkbaar met 2017, met een incidentie van 28,5 per 100.000 (4.897 gevallen) vergeleken met 28,7 in 2017 (4.912 gevallen). De incidentie bleef het hoogst in de leetijdsgroep 0 tot 5 maanden (156,9 per 100.000, 133 gevallen). Eén persoon overleed aan kinkhoest in 2018, een jonge (nog) niet gevaccineerde zuigeling. In het eerste trimester van 2019 zagen we een toename in het aantal kinkhoestgevallen (2.236 gevallen tot en met april, IR van 38,8), wat klopt met het epidemiologische patroon van kinkhoest. De toename was het grootst in de leeftijdsgroepen 0 tot 5 maanden (IR van 192,3 versus 156,9 in 2018) en 10 tot 19 jaar (IR van 91,3 versus 62,5 in 2018). Eén zuigeling en één ongevaccineerde volwassene ouder dan 80 jaar overleden begin 2019 aan kinkhoest. De prevalentie van pertactine-deficiënte stammen was 24% in 2018 vergeleken met 9,7% in 2017. Het aantal zwangere vrouwen dat zich laat vaccineren tegen kinkhoest stijgt, met een geschatte vaccinatiegraad van 13% in 2018 en 26% in 2019 (tot 1 april). De implementatie van deze maternale kinkhoestvaccinatie in het RVP is gepland voor december 2019.

Pneumokokkenziekte

Bij kinderen <5 jaar leidde de introductie van pneumokokkenconjugaat-vaccinatie (PCV) in 2006 tot een afname van invasieve pneumokokkenziekte (IPD) met 59% in 2018/2019. In 2018/19 waren er 71 kinderen <5 jaar met IPD. Sinds 2013/'14 is de IPD-incidentie bij kinderen <5 jaar echter licht toegenomen vanwege een langzame toename van IPD veroorzaakt door serotypes die niet zijn opgenomen in het 10-valent PCV. In andere leeftijdsgroepen werden vergelijkbare trends waargenomen met een zeer lage incidentie van IPD veroorzaakt door vaccin serotypen en een toenemende incidentie van IPD als gevolg van niet-vaccin serotypen, wat de algehele impact van PCV-implementatie verlaagde.
Vanaf 2020 wordt het 23-valent pneumokokkenpolysacharidevaccin (PPV23) door huisartsen aangeboden aan alle 60-, 65-, 70- en 75-jarigen in Nederland.

Polio

In 2018 en tot 1 juli 2019 zijn er geen gevallen van polio gemeld en is er geen poliovirus gedetecteerd in Nederland.
In Nigeria, één van de landen waar polio nog endemisch was, werden in 2018 en in 2019 (tot 10 juli) geen gevallen van wild-type polio gemeld. In Afghanistan en Pakistan werden gezamenlijk voor die periodes respectievelijk 33 en 42 gevallen gemeld. De eradicatie van het poliovirus wordt gehinderd door uitbraken van cVDPV in niet-endemische landen.

Rodehond

In 2018 werden geen gevallen van rodehond gemeld.
In heel Europa blijft het aantal gevallen van rodehond in 2018 dalen.

Tetanus

In 2018 is er één melding van tetanus binnengekomen. Het betrof een oudere man die geboren is voor invoering van het RVP. Volgens de LCI richtlijnen kwam hij in aanmerking voor Tetanus Toxoid en anti-Tetanus immunogobulines als post-expositie-profylaxe, maar hij heeft alleen Tetanus Toxoid ontvangen.

Het vaccinatieprogramma in Caribisch Nederland

Over het algemeen is de vaccinatiegraad in de Nederlandse overzeese gebieden, inclusief Caribisch Nederland (d.w.z. Bonaire, Sint Eustatius en Saba) hoog. In 2018 werden geen RVP-ziekten gemeld op Bonaire, Saba en Sint Eustatius.
Uit gegevens van de Health Study Caribisch Nederland is gebleken dat de totale seroprevalentie voor mazelen relatief hoog (94%), maar lager voor bof en rodehond (beide 85%). Uitbraken van mazelen en difterie, die in Venezuela zijn begonnen vanwege een humanitaire crisis, blijven voorkomen in de WHO-regio van Noord- en Zuid-Amerika.. Daarom moeten gezondheidswerkers op de eilanden in de overzeese gebieden alert zijn om gevallen te detecteren en indien nodig adequaat reageren om overdracht te voorkomen. Seroprevalentie voor varicella in Caribisch Nederland (algemeen 78%) neemt gestaag toe met de leeftijd; echter, in tegenstelling tot Nederland, langzamer en niet 100% bij ouderen. Dit resulteert in een populatie die op oudere leeftijd vatbaar is voor varicella, inclusief zwangere vrouwen en ouderen, met het potentieel om ernstigere ziekte en gevolgen te ontwikkelen.
Met ingang van 1 januari 2019 werd de toedieningsleeftijd van het booster BMR-vaccin op Bonaire verlaagd van de leeftijd van 9 jaar naar 18 maanden om tijdige bescherming van kinderen te waarborgen.

Potentiële RVP-kandidaten

Hepatitis A

Er werden in 2018 188 hepatitis A gevallen gerapporteerd. Dit is een halvering van het aantal meldingen in 2017 (n=374), maar nog steeds hoger in vergelijking met 2011-2016 (80-125 gevallen). De internationale uitbraak onder MSM was in 2017 op zijn hoogst maar er werden in 2018 nog steeds gevallen gemeld waarbij een van de drie aan deze uitbraak gerelateerde stammen gevonden was. Ongeveer driekwart van de gemelde gevallen in 2018 betrof een volwassene (≥20 jaar). 36% Van de Nederlandse gevallen was reis-gerelateerd, voornamelijk met reizen naar Marokko.

Respiratoir syncytieel virus (RSV)-infectie

In het respiratoire seizoen 2018/2019 werd in 12% van de monsters van de surveillance naar influenza-achtig ziektebeeld en andere acute respiratoire infecties RSV als verwekker aangetoond, vergeleken met 6% in 2017/2018 en 12% in 2016/2017. Een fase 3 onderzoek naar de effectiviteit van RSV-vaccinatie tijdens de zwangerschap toonde geen significant effect aan op het primaire eindpunt, namelijk medisch relevante lagere luchtweginfecties door RSV, maar de effectiviteit tegen RVP ziekenhuisopnames werd geschat op 44,4% (95%BI 19,6-61,5%) en tegen RSV ziekte met ernstige hypoxemie op 48,3% (95%BI -8,2-+75,3%). Een fase 2 onderzoek naar de effectiviteit van een langwerkend immuunglobuline gaf 70,1% daling van het risico op medisch relevante lagere luchtweginfecties door RSV.

Rotavirusinfectie

In 2018 zijn er in Nederland 1.129 rotavirusdetecties gerapporteerd, wat iets meer is dan in 2017 (n=1.047). Na uitzonderlijk lage rotavirusseizoenen in 2014 (n=607 detecties) en 2016 (n=679 detecties), waren de rotavirusseizoenen in 2017 en 2018 vergelijkbaar. Dit is in tegenspraak met de eerdere hypothese van een overgang naar een tweejaarlijks patroon. Tot half juli 2019 zijn er iets minder gevallen van rotavirus geobserveerd in vergelijking met dezelfde periode in 2018 (2018: n=1033; 2019: n=911). De helft van alle getypeerde monsters in 2018 betrof rotavirus serotype G9 (89/179). De meeste geïdentificeerde genotypen waren G9P8 (60/179) en G3P8 (56/179). Het ministerie van Volksgezondheid, Welzijn en Sport heeft in juli 2018 besloten dat hoge risicokinderen gevaccineerd moeten worden tegen rotavirus via het RVP. De implementatie van dit plan loopt.

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

De epidemiologie van VZV (huisartsenbezoeken, ziekenhuisopnames en sterfgevallen) is vergelijkbaar met voorgaande jaren: in 2017 werden door huisartsen ongeveer 48.000 waterpokken- en 90.000 gordelroosepisodes gerapporteerd (respectievelijk 280 en 530 episodes per 100.000 inwoners).

In juli 2019 heeft de Gezondheidsraad positief geadviseerd over het vaccineren van ouderen tegen gordelroos met het nieuwe Shingrix®-vaccin. Volgens de Gezondheidsraad mag de kosteneffectiviteit van vaccinatie de gebruikelijke referentiewaarde van €20.000 per QALY echter niet overschrijden, wat niet het geval is bij de huidige 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) to all children born from 1945 onwards in a programmatic approach. 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.

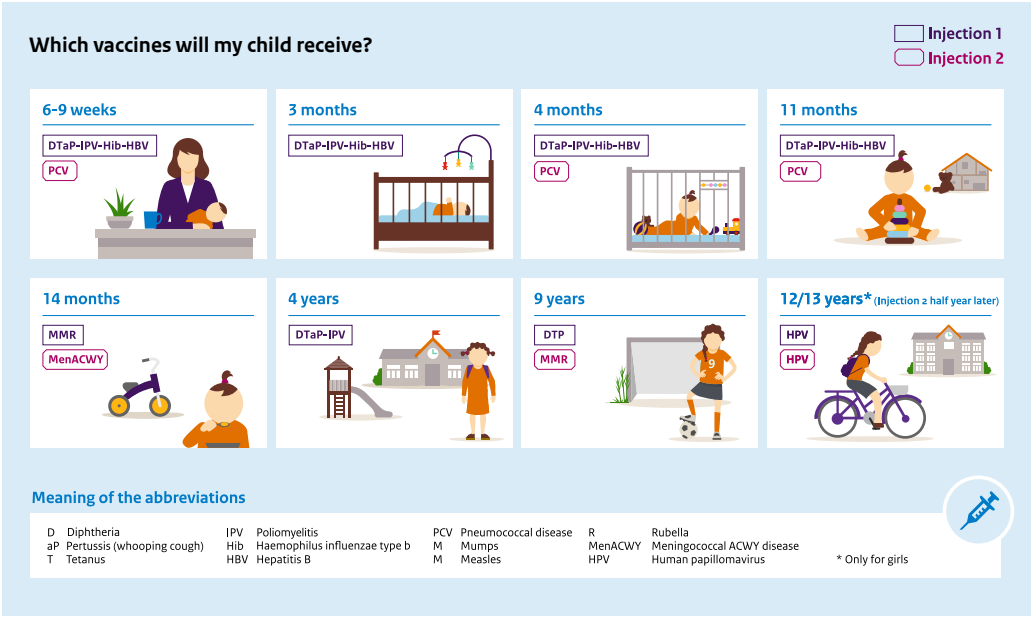


Figure 1.1 NIP vaccination schedule
Source: *http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals*

1.1.1 Changes in the vaccination schedule

Starting 1 May 2018, a MenACWY vaccine was substituted for MenC vaccine at 14 months of age. In October 2018, adolescents born between 1 May 2004 and 31 December 2004 were offered MenACWY vaccination.

1.1.2 Number of vaccinated children

In 2018, the vaccination schedule consisted of 12 (boys) or 14 (girls) vaccine doses per child. Of these, 7 were given between 0 and 11 months.

In 2018, almost 880,000 children aged 0 to 19 years were immunised under the Dutch NIP. Together they received a total of 2,266,000 vaccine doses. This is more than in previous years because of the additional MenACWY campaign for adolescents.

1.2 New recommendations and decisions

1.2.1 New decisions of the Ministry of Health, Welfare and Sport

In July 2018, the State Secretary responsible for the NIP decided to extend the MenACWY vaccination outbreak programme. In 2019, all 14-18-year-olds (birth cohorts 2001-2005) will be offered the vaccination.

Furthermore, the State Secretary decided that vaccination against rotavirus-caused diseases will only be included in the NIP for infants at increased risk, and that NIP maternal pertussis vaccination will be organised by the youth healthcare organisations.

1.2.2 New recommendations from the Health Council of the Netherlands

In December 2018, the Health Council of the Netherlands recommended implementing MenACWY vaccination in the NIP for 14-year-olds and continued MenACWY vaccination at 14 months of age [1]. The Health Council did not recommend adding MenB vaccination to the NIP in view of the uncertainty concerning the effectiveness of the vaccine and because it can cause high fever, especially in infants and when administered in combination with other routine vaccines. In addition, the cost-effectiveness of MenB vaccination is highly unfavourable compared to the commonly used reference value of €20,000 per quality adjusted life year. The Council recommended a review when new data becomes available.

The Health Council recently recommended adapting the vaccination schedule for infants in relation to maternal pertussis vaccination. If a mother is vaccinated, her child is also protected from birth. As a result, the first vaccination can be postponed and the number of doses reduced from three to two [2]. Before the maternal pertussis programme starts in December 2019, the Health Council will advise whether the maternal pertussis vaccination can be given from 22 weeks gestational age onwards.

Due to the availability of the new Shingrix® vaccine, the Health Council published a new advisory report on vaccination against HZ in July 2019. In principle, the Health Council issues a positive recommendation with regard to vaccinating the elderly against HZ with this new vaccine. However, the disease burden of HZ is relatively low compared to other diseases, such as pneumococcal disease and influenza. The Health Council therefore considers it important that the cost-effectiveness of vaccination does not exceed the commonly used reference value of €20,000 per QALY. To achieve that goal, the price of the vaccine should be reduced considerably [3]. At present, the vaccine is not available in the Netherlands (*https://www.rivm.nl/gordelroos/gordelroosvaccinatie*).

Furthermore, the Ministry of Health, Welfare and Sport decided to offer HPV vaccination to boys in addition to girls as recommended by the Health Council. Vaccination will be given close

to the age of nine years. They are also looking into the options for offering unvaccinated boys and girls the vaccination up to 26 years of age [4].

The Health Council is currently preparing a recommendation on the target groups for influenza vaccination and the safety and effectiveness of new vaccines. Pregnant women and children are potential new target groups [5].

1.3 Vaccination of risk groups

Influenza vaccination is offered to people aged 60 years and over, and to those with an increased risk of morbidity and mortality following influenza, through the National Influenza Prevention Programme (NPG). Vaccination against tuberculosis is offered to children of immigrants from high-prevalence countries. For developments with regard to influenza and tuberculosis, please refer to the reports issued by the Centre for Infectious Disease Control (CIb), the Health Council, and the KNCV Tuberculosis Foundation [6-9].

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 prostitution is in place in the Netherlands [10].

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. These vaccinations are paid for by the recipient. Relevant information 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 adults, 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 for herpes zoster vaccination, maternal pertussis vaccination, pertussis vaccination for adults, HPV vaccination outside the NIP, meningococcal ACWY vaccination, meningococcal B vaccination, rotavirus vaccination, varicella vaccination, pneumococcal vaccination for the elderly, hepatitis B vaccination and hepatitis A vaccination are also available at *https://lci.rivm.nl/richtlijnen/*. Additionally, guidelines for vaccination of medical risk groups, such as patients with aspleny, are in place.

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*RIVM publication

2
Vaccination coverage

E.A. van Lier

2.1 Key points

- The decline in vaccination coverage has come to an end; vaccination coverage for most vaccinations has remained roughly the same as in the previous year.
- Provisional figures for younger children show a slight increase.
- The provisional national vaccination coverage for the new meningococcal ACWY vaccination for adolescents is high (87%).

2.2 Tables and figures

Table 2.1 Vaccination coverage (%) per vaccine for age cohorts of newborns, toddlers, schoolchildren and adolescent girls in 2006–2019 [1]

Reporting year	Newborns*							
	Cohort	DTaP -IPV	Hib	HBV [a]	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
2019	**2016**	**92.4**	**93.1**	**92.0**	**92.6**	**92.9**	**92.6**	**90.2**

Table continued on next page

Reporting 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
2019	**2013**	**90.3**	**2.2**	**92.5**	**2008**	**89.5**	**89.5**	**2004**	**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. Universal hepatitis B vaccination was introduced in 2011; 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

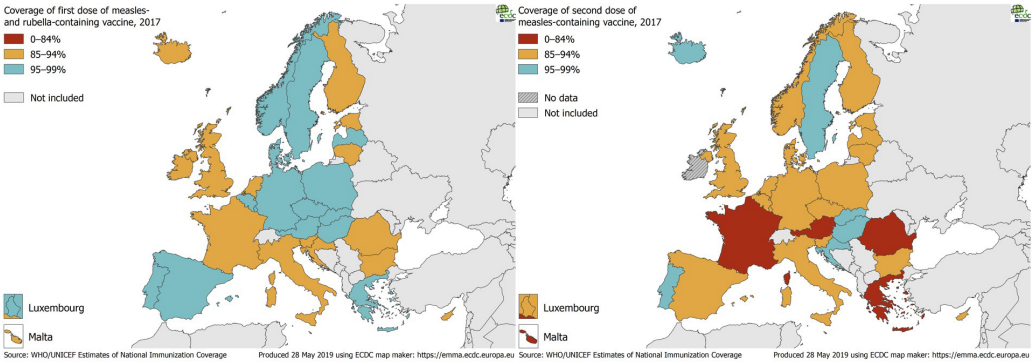

Figure 2.1 Vaccination coverage for first (left) dose of measles and rubella-containing vaccine and second (right) dose of measles-containing vaccine, EU/EEA, 2017 [3]

2.3 Vaccination coverage

The decline in vaccination coverage, i.e. the proportion of children who receive vaccinations through the NIP, has ceased. Overall national vaccination coverage is not yet back to the old level, but has remained roughly the same as in the previous year for most vaccinations. Provisional figures for younger children show a slight increase [1].
At 45.5%, the national vaccination coverage for HPV (cervical cancer) remained the same as the previous year and it does seem to be increasing for younger girls. Provisional figures showed that among girls born in 2006 almost 65% received a first HPV vaccination [2], compared with 44%-47% for girls born in the period 2003-2005. The provisional national vaccination coverage for the new meningococcal ACWY vaccination for adolescents is high (87%) [1].
The State Secretary for Health, Welfare and Sport wants to give 16 or 17-year-olds the opportunity to catch up with NIP vaccinations they previously did not receive. Approximately one tenth of all boys are eligible. It applies to about half of the girls, mainly due to the HPV vaccination [1].

The WHO announced that in 2018, measles killed 72 children and adults in the European region, and over 80,000 measles cases were reported in 47 out of 53 countries. This is the highest annual number in the present decade; three times the number of cases in 2017 and 15 times that in 2016. These figures highlight that although measles vaccination coverage has improved overall in the region, many people remain susceptible. The estimated coverage for the second dose of measles vaccine was below the 95% threshold to achieve herd protection in 34 countries in 2017 [4].
Only four countries (Hungary, Portugal, Slovakia, and Sweden) in the European Union/ European Economic Area (EU/EEA) reported at least 95% vaccination coverage for both the first and second doses in 2017 (see Figure 2.1) [3]. In 2017, vaccination coverage rose for the first dose to above 95% in Denmark and Latvia and dropped for the second dose to below 95% in Spain compared to 2016.

Therefore, in different surrounding countries, the discussion about whether or not to introduce mandatory vaccination is still going on although there is uncertainty about its effectiveness [5]. In Italy vaccination against pertussis, measles, mumps, rubella (MMR), varicella, and Hib was added to the list of mandatory vaccinations (diphtheria, tetanus, hepatitis B, and polio) in July 2017. From 2016 to 2017, vaccination coverage for measles at 24 months of age increased by 4.4%, most likely as a result of the new law supported by the related media campaign [6]. From 2017 to 2018 coverage increased further by 2.3% to reach 94.1% (preliminary data) [7]. In France, mandatory vaccination was extended from three (diphtheria, tetanus, and poliomyelitis) to all eleven vaccinations of the NIP schedule in December 2018. The vaccination coverage for MMR at 14 months of age increased by 3% to 77.7% between 2017 and 2018; the final coverage at 24 months of age will be higher due to the usual catch-up in the second year of life [8].
Recently, Germany announced that, because of the increase in measles cases in recent years, vaccination against measles will be mandatory for children going to school or daycare. This will also apply to teachers, healthcare personnel and people who work in refugee aid. Furthermore, after the introduction of a new law, parents in the state of New York can no longer refuse vaccination against measles for religious reasons for their school-going children due to the recent measles outbreak in New York. In the Netherlands, vaccination coverage with voluntary vaccination is still high from the international perspective, with the exception of HPV vaccination.

2.4 Literature

2.4.1 References

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*RIVM publication

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3
Acceptance of vaccination

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3.1 Key points

- Approximately 70% of pregnant women have heard of maternal pertussis vaccination (MPV). About 60% have a positive intention to receive MPV, 25% are neutral and 15% have a low intention.
- The extent to which mothers completed the intervention, a tool developed for mothers to help make a decision on HPV vaccination for their daughters, had a positive impact on their daughters' vaccination uptake.
- A biology curriculum was developed for younger high school students.

3.2 NIP acceptance monitoring

The decline in the NIP vaccination coverage in the Netherlands has come to an end (cf. chapter 2). Most parents vaccinate their children according to the NIP, with the exception of HPV vaccination for girls. It remains important to monitor and explore reasons that influence the willingness to vaccinate. Developments in the vaccination program, cover a lifespan; pregnancy (maternal pertussis vaccination will be implemented in December 2019 focusing on unborn babies), infancy, adolescents and elderly (pneumococcal vaccination for elderly will start in 2020).
In a separate section, developments regarding communication will be presented.

3.3 Pregnancy (pre-birth)

3.3.1 Maternal pertussis vaccination

A study conducted end of 2018/early 2019 (N = 942 among which 358 pregnant women and 584 women with a child of two years or younger) examined whether women received the maternal pertussis vaccine and whether or not they had heard or read about maternal pertussis vaccination (MPV). Approximately 70% of pregnant women reported having either heard or read about the maternal pertussis vaccination. This is somewhat higher compared to other another study [1]. About 37% reported having searched actively for more information about MPV. Pregnant women in this study were, on average, 21 weeks pregnant (range 2 - 45 weeks) and 60% had a positive intention toward MPV, 25% were neutral and 15% had a low intention. In this study selecting the women who were, at that time, eligible to receive the maternal pertussis vaccine (e.g. at least 28 weeks pregnant) shows nearly 46% being vaccinated. This is somewhat higher than estimated for the Netherlands from vaccination data retrieved from the Foundation for Pharmaceutical Statistics (SFK) and municipal health services (13% and 26% in 2018 and 2019, respectively, see chapter 7.8). The most common reason for pregnant women to refrain from the vaccination was a lack of information (i.e. they did not know the maternal pertussis vaccine existed at the time they were pregnant).
In addition, many pregnant women reported they were planning on getting the vaccination,

but they were too early on in their pregnancy to be eligible for vaccination. Most pregnant women trusted the information about MPV provided by the RIVM, midwives, and youth healthcare (respectively 79%, 78% and 70% of the pregnant women).

3.4 Infants

In 2017, 2,556 parents with a child between the ages of 2 and 4 years completed a questionnaire about accepting, refusing or partially accepting childhood vaccinations. Thirty-five per cent of these parents made an informed decision about childhood vaccination. This percentage amounted to 54% for parents who accept childhood vaccinations (acceptors), 18% for parents who refuse childhood vaccinations (refusers), and 35% for parents who partially accept childhood vaccinations (partial acceptors). Lack of evidence-based knowledge and a lack of deliberation about the pros and cons of vaccinating had the greatest impact on informed decision-making.
Parents who refuse or partially accept childhood vaccinations for their child based their decision on cognitive beliefs, which are not in line with scientific evidence about childhood vaccination. Although these parents do not meet the definition of informed decision-making, they feel more informed regarding childhood vaccination than parents who accept or partially accept childhood vaccinations (refusers: scored 83 out of 100 on a scale regarding feeling informed, acceptors: scored 70 out of 100, partial acceptors: scored 70 out of 100, regarding their feeling of being informed about childhood vaccination, $p<0.01$). Furthermore, parents who refuse childhood vaccination showed less decisional conflict (i.e. doubts about their decision) than acceptors and partial acceptors (Refusers: scored 20 out of 100, acceptors: scored 23 out of 100, partial acceptors: scored 28 out of 100, $p<0.01$). To reduce decisional conflict about childhood vaccination it is important to reduce barriers associated with decision-making, increase trust in (information about) the NIP, and strengthen and/or discuss existing beliefs [2, 3].

3.5 Adolescent

3.5.1 HPV vaccination

To improve vaccination acceptability and informed decision-making, a web-based tailored intervention was developed [4]. Part of this intervention was providing mothers with statistical information on HPV (i.e. factual epidemiological information about the prevalence of HPV and cervical cancer, and the expected reduction in cervical cancer cases if all girls would receive the HPV vaccination). This information increased mothers' perceptions of their daughters' susceptibility with regard to HPV [5]. Another study focused on the effectiveness of this intervention in increasing vaccination acceptance and improving informed decision-making. The authors reported that the extent to which mothers finished the intervention had a positive impact on the vaccination uptake of their daughters (i.e. mothers who had completed more of the intervention were more likely to have their daughter vaccinated against HPV) [6].
An overview of interventions to increase HPV vaccination coverage and how HPV vaccination is organised in other countries was made. This overview shows that in EU/EEA countries, the age at which girls receive vaccination varies between 9 and 15 years. Also, the place of

administering vaccines varies from school, public or private practices, or a combination thereof. In Ireland and Denmark, HPV vaccination coverage had also dropped steeply. The authorities therefore developed tailored information for public and professionals, set up an alliance with various stakeholders, and were active on social media. A literature review shows that making use of reminders (before the vaccination moment), no-show (after vaccination moment if they did not show up), tailored information, providing feedback of vaccination coverage to child vaccine providers and making it easier to get the vaccination, could result in an increase of HPV vaccination coverage reaching 10% to 20%. It remains important for healthcare workers to recommend vaccination and refute misperceptions about HPV vaccination [7].

3.6 Communication

Several means of communication have been developed or are being upgraded by the RIVM. There is a shift in the goals of the communication strategy. Previously, the main focus was on 'informing' and 'creating trust', however 'activating' has become an increasingly important goal. This transition is complex. In collaboration with the Ministry of Health, Welfare, and Sport the CASI instrument (i.e. communication activation strategy instrument) will be used. The goal is to create a robust NIP which is prepared for challenges in the future. Furthermore, the use of social media is becoming increasingly important. A specialist monitors the questions on Facebook, twitter and Instagram, provides quick answers, and/or corrects wrong or incomplete information.
People who have personal experience with diseases and/or vaccination play a larger role in conveying the message of the RIVM by telling about their experiences and reasons for vaccinating themselves and/or their children. Communication also becomes increasingly dependent on images and less on text. This trend will continue in the coming year(s). In 2018, the RIVM published several infographics to complement reports. A new step in 2018 was the development of a biology curriculum for high school students (year 3 and up) on vaccination, the immune system and pathogens. In 2019, there will also be a curriculum for younger high school students.
Another development driven by the State Secretary is a so-called 'vaccination alliance'. This alliance of researchers, HCPs, communication experts and policy makers will discuss several measures proposed by the State Secretary, such as connecting research, education and communication more intensively, actively countering misinformation, empowering the role of HCPs, and possibilities to catch up on (missed) vaccinations. Topics that receive special attention are HPV vaccination and research focusing on solutions regarding infant daycare (i.e. refusing of unvaccinated children at daycarecenters). Furthermore, HCPs involved in the NIP have been provided with more time to educate people on the NIP and answers questions they may have regarding vaccination.

A case study on vaccination was conducted to illustrate how digital methods can be used for tailoring communication towards different communities by detecting online communities, mapping health–related norms and perceptions per community, and identifying social influencers as potential collaboration partners [8]. Examples of online communities that were

identified in the study are healthcare, anti-establishment, Dutch/Flemish and alternative media. Furthermore, at the center of these communities, the reserarchers identified a "core-community" (e.g. nucleus community). The nucleus community represents the space where health communities and anti-establishment community engage with a general audience. It consists of politicians, media and communication professioanls and a mix of profiles that seem to be rooted in one fo the surrounding communities. Most of the themes, frames and narratives, that originate in the healthcare and anti-establishmentcommunities, are discussed in this nucleus community. This resulted in a mix of frames in favour of and against vaccination. Results from mapping the discourse on vaccination in and between communities can be used to define and tailor health communications to the perceptions of these communities. Furthermore, it can be used to decide which frames to support and which misconceptions to address. The study showed many potential collaboration partners about vaccination, such as a data blogger (role: opinion leader; goal: sharing fact-based information), a podcast host (role: opinion leader; goal: sparking conversation), and a political blogger (role: gatekeeper; goal: sharing different perspectives). In this way, health-related communication professionals and social influencers can collaborate effectively to create health interventions that are tailored to the preferences, perceptions and cultures of these online communities.

3.7 International literature

3.7.1 Maternal pertussis vaccination

A systematic review conducted in England aimed to identify strategies to increase the uptake of vaccination during pregnancy in high-income countries. Most included papers were conducted in the US and focused on increasing influenza vaccination during pregnancy.
A number of strategies has been shown to be effective: reminders about vaccination on antenatal healthcare records, midwives providing vaccination, and providing education and information for healthcare professionals (HCP) and the target group [9]. This need for education and information is also demonstrated in other studies [10, 11].
Research conducted in Ireland showed that despite awareness of both influenza and pertussis vaccination during pregnancy, the uptake was low (respectively 42,5% and 31%). The main reasons for not being vaccinated reported by pregnant women were safety concerns and inadequate information from their HCP [10]. Another study concluded that both HCPs and pregnant women should continue to be educated on the importance and safety of the appropriate immunisations during pregnancy [11].

3.7.2 Rotavirus vaccination

A global survey showed that rotavirus vaccination coverage varies widely across the world, sometimes even within the same geographical area (from 0 to 90%) [12]. Elevated costs of immunisation and a misperception about the severity and consequences of a rotavirus infection are reported as major barriers to universal distribution. Awareness of these barriers can drive vaccination uptake.
A study conducted in Italy supports these findings as it showed that parents were more likely to have their child vaccinated if they considered it dangerous for their child to contract rotavirus gastroenteritis, thought the rotavirus vaccine useful, and received information by a

physician [13]. To date, no more than a few studies worldwide have examined what parents know, believe and experience with regard to this topic [13-15]. These studies show that awareness of rotavirus infection and RV vaccination and universal implementation increase parents' knowledge and attitudes towards the rotavirus vaccine. Furthermore, support should be offered to the physicians regarding their key role in achieving public acceptance of new vaccines.

3.7.3 HPV vaccination

Human papillomavirus (HPV) vaccination uptake remains low. Most research and reviews have focused on HPV vaccination for girls. A review and meta-analysis focusing on HPV vaccination among US children, adolescents, and young adults aged 9-26 years supports previous evidence that behavioural and informational interventions (e.g. decision support materials such as educational messaging/video, educational websites tailored to baseline knowledge brochures/factsheets) are effective in vaccine initiation and behavioural interventions for completion [16]. Furthermore, it shows that more information is needed on culturally appropriate interventions to reach a more diverse population. This may also include HPV vaccination for boys. A review emphasises that providing clear and unambiguous messages about HPV vaccines (i.e. for whom, boys or girls), for what (i.e. genital warts and cancers in men), and when (before sexual debut) through increased HCP-initiated discussion and targeted public health campaigns may support HPV vaccine among boys [17].

3.7.4 Pneumococcal vaccination

A systematic review aimed to understand and identify potential factors influencing pneumococcal vaccination acceptance among the adult community [18]. The review states that several factors influence the acceptance of pneumococcal vaccination, such as not widely promoting or recommending the vaccination to the public. One of the main factors found to influence acceptance was the perception of the individual. Good perception was identified as the person believing that the vaccination might prevent invasive pneumococcal disease. Negative perceptions focused more on possible side effects and the effectiveness of the vaccine. Furthermore, the review showed that the most significant factor contributing to acceptance of pneumococcal vaccination is a history of influenza vaccination.

3.7.5 Communication

How the media constructs and frames messages about vaccination programmes is a key determinant in public approval of vaccinations, according to health communication experts. An international review examined the media coverage of vaccines within traditional media (e.g. television, radio, newspapers, magazines, medical journals, books, pamphlets, and movies) [19]. Most studies were conducted in the U.S. The review focused on traditional media as it still plays an important role and is even considered a central medium in the communication landscape, despite the rapid growth of the internet and social media. They state that traditional media outlets are accessed more intensively than digital media in the U.S., and in some countries, like Sweden, newspapers are highly consumed by society. The review showed that with regard to media content, most studies found negative messages about vaccination and identified a lack of accurate information. Journalist and editors want a

good story and might not put public health first or devote much attention to it in the first place. However, media space constraints also pose challenges to extensive explanations. This is alarming, as the media remain an important source of health information [19, 20]. The level of accuracy and evidence-based information provided are other key outcomes. According to the selected studies, there is a lack of comprehensive information, as well as inaccuracies and errors in both fact and logic, leading to the conclusion that journalists tend to misrepresent the state of clinical evidence. It is important to avoid the transmission of inaccurate information to prevent misinterpretation and negative decisions about getting vaccinated. Improving communication between health officials and journalists has been a useful strategy. Furthermore, the review states that misinformation of the public by the news media leads to misperceptions of reality among their audience and also affects trust and credibility. Without trust and credibility, the audience turns to other information suppliers [19].

The CDC webpage contains a section called 'what parents need to know about vaccines' (*https://www.cdc.gov/vaccines/growing/*). Furthermore, there is a report 'Wellcome' on trust in science and health, which also focuses on vaccinations (*https://wellcome.ac.uk/sites/default/files/wellcome-global-monitor-2018.pdf*). It states that most people (around 72%) in high-income regions (e.g. Northern America and Northern Europe) agree that vaccines are safe. However, in Western Europe (especially in France) this figure is lower, around 59%. In lower-income regions this proportion is much higher (around 93%). Worldwide, 92% of parents said their children had received a vaccine to prevent them from getting childhood diseases, while 6% said they did not and 2% said they did not know. In the Netherlands 91% strongly or somewhat agreed with the statement that vaccines are important for children to have, and 11% strongly or somewhat disagreed that vaccines were effective. When people have high trust in HCPs, they are most likely to consider vaccines safe. There seems to be a positive relationship between overall trust in scientists and attitudes towards vaccines, but his relationship is strongest in high-income countries (also in the Netherlands).

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4
Burden of disease

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4.1 Key points

- The estimated burden of disease caused by (partially) vaccine-preventable diseases expressed in Disability Adjusted Life Years (DALYs) for the year 2018 was highest for HPV (based on the burden in 2017 instead of 2018: 18,000 DALYs (75% among women) invasive pneumococcal disease (10,800 DALYs/year), pertussis (2,000 DALYs/year), rotavirus infection (1,200 DALYs/year), invasive meningococcal disease (1,100 DALYs/year), and invasive *Haemophilus influenzae* disease (1,000 DALYs/year).
- For most diseases, the estimated burden in 2018 was comparable to the estimated burden in 2017. The burden for hepatitis A was lower in 2018 than in the outbreak year 2017.

4.2 Tables and figures

Table 4.1 Estimated annual disease burden in DALYs in 2014–2018, and DALYs per 100 infections in 2018 in the Netherlands (with 95% uncertainty intervals) [1, 2]

Disease	DALYs (95% uncertainty interval)					DALYs/100 infections
	2014	2015	2016	2017	2018	
Diphtheria	1 (1–2)	4 (3–5)	2 (2–3)	4 (3–4)	3 (3–4)	110 (91–130)
Hepatitis A virus infection	57 (35–94)	43 (27–72)	44 (27–73)	200 (120–340)	100 (62–170)	11 (8–15)
Hepatitis B virus infection (acute)	250 (230–260)	100 (94–110)	180 (170–190)	150 (140–160)	130 (120–140)	21 (20–23)
Human papillomavirus infection[a]						
• Females	12,300 (11,500–13,100)	12,000 (11,200–12,800)	12,500 (11,800–13,400)	13,500 (12,700–14,300)		n.a.
• Males	4,700 (3,800–5,700)	4,900 (4,100–5,900)	5,000 (4,100–6,100	4,500 (3,700–5,400)		n.a.
Invasive *H. influenzae* disease	690 (650–730)	840 (800–890)	860 (800–910)	980 (930–1,000)	1,000[b] (960–1,100)	380 (360–400)
Invasive meningococcal disease	590 (460–730)	560 (440–700)	880 (730–1,000)	1,100 (970–1,300)	1,100[c] (960–1,300)	520 (480–570)
Invasive pneumococcal disease	9,100 (8,500–9,600)	10,900 (10,200–11,500)	9,800 (9,200–10,400)	9,800 (9,200–10,400)	10,800[d] (10,100–11,400)	350 (330–370)
Measles[e]	28 (26–31)	1 (1–1)	1 (1–1)	3 (2–3)	5 (4–5)	2 (2–2)
Mumps	0.3 (0.3–0.3)	0.7 (0.6–0.7)	0.5 (0.5–0.6)	0.4 (0.3–0.4)	0.6 (0.5–0.6)	0.4 (0.4–0.4)
Pertussis	3,600 (3,300–3,900)	2,700 (2,500–2,900)	1,500 (1,400–1,600)	2,000 (1,900–2,200)	2,000 (1,900–2,100)	1 (1–1)
Poliomyelitis	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	n/a
Rabies	49 (49–49)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	n/a
Rotavirus infection	600 (250–1,200)	1,300 (520–2,500)	670 (280–1,300)	1,100 (440–2,200)	1,200 (470–2,400)	0.5 (0.3–0.9)
Rubella	210 (170–260)	0.06 (0.04–0.08)	0 (0–0)	0 (0–0)	0 (0–0)	n/a
Tetanus	0 (0–0)	9 (7–10)	9 (2–2)	0.6 (0.5–0.8)	1 (1–1)	97 (93–100)

DALY= disability-adjusted life years

n/a = not applicable; no cases occurring in 2018 or unknown number of infections (HPV)

[a] Annual burden estimates not available for 2018. To estimate the burden, the numbers of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV were used. As the incidence of anogenital warts could not yet be estimated for the year 2017, the incidence for 2016 was carried over to 2017.

[b] Proportion caused by the vaccine-preventable type b in 2018: 28%.

[c] Proportion caused by the vaccine-preventable type C in 2018: 1%; proportion caused by type B in 2018: 47%; proportion caused by type W in 2018: 42%.

[d] Proportion caused by the vaccine-preventable types 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F in 2018: 10%.

[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

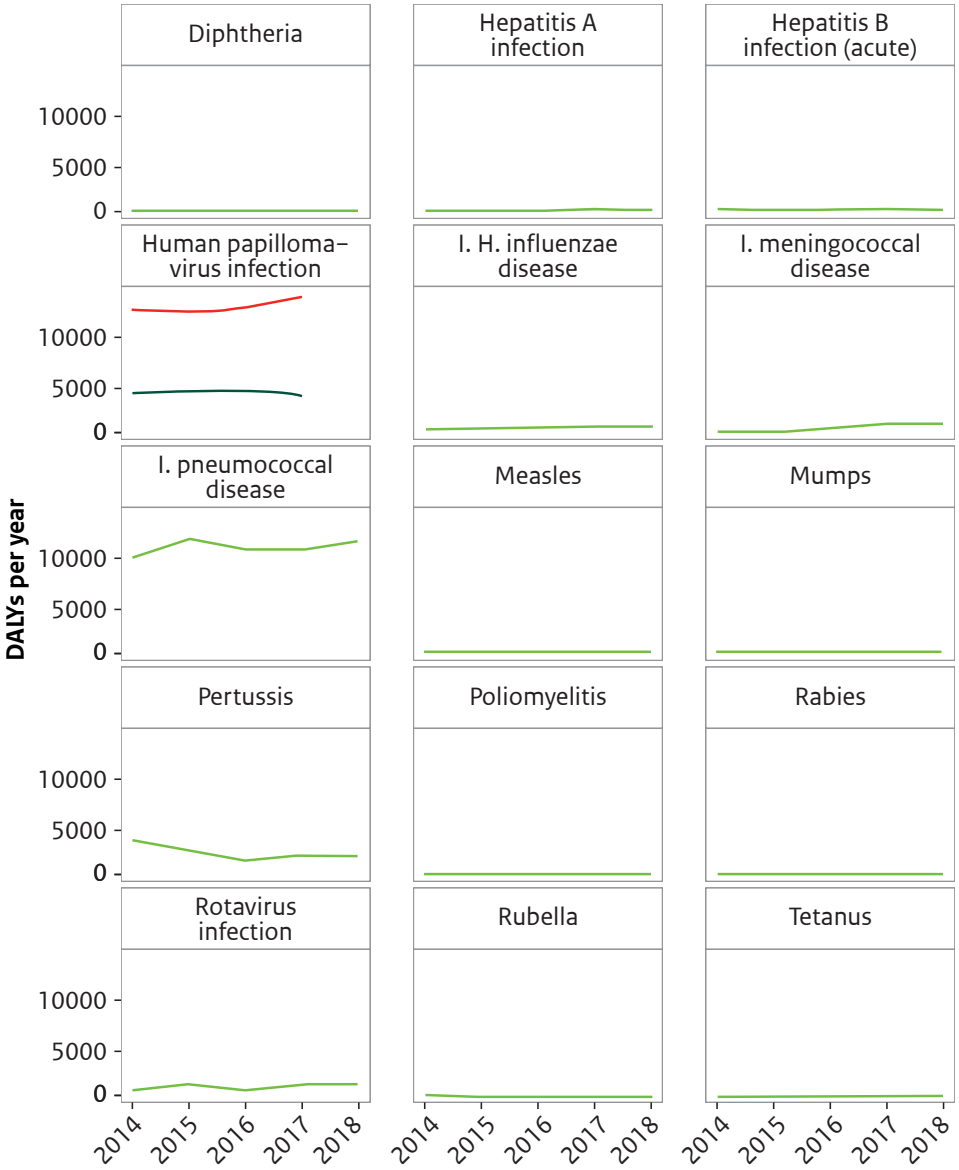


Figure 4.1 Estimated annual disease burden in DALYs in 2014–2018 in the Netherlands [1, 2]

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 (DALYs) of vaccine-preventable diseases in the period 2014–2018. We present the same estimates published in the 'State of infectious diseases in the Netherlands, 2018', in which more detailed information on the parameters used can be found [1]. Estimates for human papillomavirus (HPV) infection were derived from a separate analysis [2] and updated for more recent years using the Global Burden of Disease (GBD) 2010 life expectancy. Note that the calculation method used for HPV is not fully comparable to that for other diseases: instead of using the number of incident infections (which are unknown), the number of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV were used. All DALY estimates were rounded up or down: 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 DALYs per year in the period 2014–2018 and the DALYs per 100 infections in 2018 (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 2018 was zero because no cases were reported. For mumps, tetanus, diphtheria, and measles, the disease burden in 2018 was estimated to be very low, while the highest burden was estimated for HPV infection (based on the burden in 2017 instead of 2018), followed by invasive pneumococcal disease, pertussis, rotavirus infection, invasive meningococcal disease, and invasive *Haemophilus influenzae* disease.

The incidence of pertussis and rotavirus infection is known to surge every few years (Figure 4.1). For most diseases, the estimated burden in 2018 was comparable to the estimated burden in 2017. For hepatitis A, the burden in 2018 was lower than in the outbreak year 2017. For invasive meningococcal disease, the burden in 2018 was still relatively high because of the continuing rise in the number of patients caused by serogroup W since October 2015. Although the burden of overall invasive meningococcal disease was the same in 2018 and 2017, the burden of meningococcal W disease was somewhat higher in 2018 than in 2017 because of the increase in cases with meningococcal W disease (480 vs 410 DALYs).

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 2014–2018, 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, Schimmer B, Mooij SH, Raven CFH, Leenstra T, Hahné SJM. State of Infectious Diseases in the Netherlands, 2018. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2019. RIVM report 2019-0069.

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

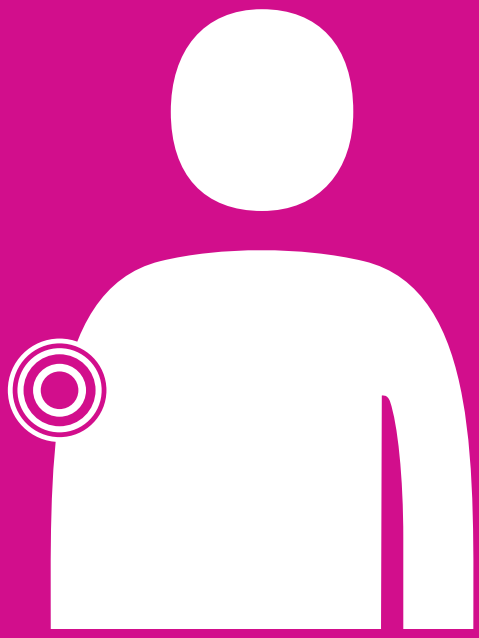
4.4.2 Other recent RIVM publications

1. de Gier B, van Kassel MN, Sanders EAM, van de Beek D, Hahne SJM, van der Ende A, et al. Disease burden of neonatal invasive Group B Streptococcus infection in the Netherlands. PLoS One. 2019;14(5): e0216749.

2. van Lier A, de Gier B, McDonald SA, Mangen MJ, van Wijhe M, Sanders EAM, et al. Disease burden of varicella versus other vaccine-preventable diseases before introduction of vaccination into the national immunisation programme in the Netherlands. Euro Surveill. 2019;24(18):pii=1800363 (see paragraph 9.4).

3. McDonald SA, Nijsten D, Bollaerts K, Bauwens J, Praet N, van der Sande M, et al. Methodology for computing the burden of disease of adverse events following immunization. Pharmacoepidemiol Drug Saf. 2018;27(7):724-30.

5
Adverse events



J.M. Kemmeren

5.1 Key points

- In 2018, Lareb received 1,519 reports of a total of 5,208 adverse events following immunisation (AEFIs). Compared to 2017, the number of reports increased by 9.8%, while the number of reported AEFIs decreased by 4.0%. The increase in number of reports is due to the introduction of the MenACWY vaccination in adolescents.
- No new signals of disturbing adverse events were found.

5.2 Tables and Figures

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

Vaccines	Total 2017	Total 2018	2m	3m	4m	11m	14m	4yr	9yr	12-13yr	14 yr	Other/ Unknown
Infanrix hexa® + Synflorix®	456	**457**	184		100	158						15
Infanrix hexa®	109	**118**	2	61	4	10						41
Synflorix®	11	**9**	1		4	2						2
MMRvaxPro® + NeisVac-C®	191	**85**					81					4
MMRvaxPro® + Nimenrix®		**173**					173					
MMRvaxPro®	19	**16**					1		1			14
NeisVac-C®	3	**1**					1					
Nimenrix®		**121**					7				62	52
Infanrix-IPV®	219											
Boostrix® Polio	172	**326**						326				
MMRvaxPro® + DTP-NVI	19											
Revaxis® + MMRvaxPro®	83	**103**							103			
DTP-NVI												
Revaxis	6	**7**							6			1
Cervarix®	85	**81**								65		16
Other	10	**22**										22
Total 2018		**1519**	187	61	108	170	263	326	110	65	62	167
Total 2017	1383		216	73	94	154	200	387	106	77		76
Total 2016	1483		174	60	95	126	171	572	84	146		55
Total 2015	1494		173	69	87	142	208	422	88	257		48
Total 2014	982		148	64	74	101	139	274	108	59		15
Total 2013	1212		217	118	75	118	133	335	92	82		42
Total 2012	1387		250	154	110	103	138	423	52	104		53
Total 2011	1103		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	14yr	Other/ unknown	Total
Rash, eczema	14	5	10	22	95	6	18	4	0	24	198
Respiratory symptoms, decreased consciousness	28	6	9	2	4	15	6	9	4	8	91
Collapse, (pre)syncope, drop attacks	3	1	1	0	1	13	6	7	3	6	41
Apnoea, dyspnoea, irregular breathing	5	3	4	0	2	2	0	2	1	2	21
Hypotonic-Hyporesponsive Episode (HHE)	15	1	4	0	0	0	0	0	0	0	20
Breath holding spells	1	0	0	1	0	0	0	0	0	0	2
Apparent Life Threatening Event (ALTE)	4	1	0	1	1	0	0	0	0	0	7
Extensive swelling of vaccinated limb (ELS)	1	2	3	7	1	21	3	0	0	11	49
Convulsions, epilepsy	5	0	3	10	25	5	3	3	0	7	61
(Febrile) convulsions, seizures	4	0	1	10	21	4	1	1	0	5	47
(Febrile) delirium	0	0	0	0	0	1	2	0	0	0	3
Epilepsy, status epilepticus	0	0	0	0	2	0	0	1	0	0	3
Ataxia, spasms, tics	1	0	2	0	2	0	0	1	0	2	8
Fever ≥40.5°C ≤42°C	2	1	4	4	17	4	0	0	0	7	39
Allergic reaction, anaphylaxis	1	0	0	8	5	4	3	2	3	8	34
Persistent crying	2	0	4	1	0	0	0	0	0	0	7
Skin discolouration	7	1	8	2	1	0	0	0	0	1	20
Abscess	1	0	0	2	4	0	0	0	0	0	7
Injection site abscess	1	0	0	2	1	0	0	0	0	0	4
Lymph node abscess	0	0	0	0	2	0	0	0	0	0	2
Abscess of salivary gland	0	0	0	0	1	0	0	0	0	0	1
Immune mediated disorders	0	1	0	0	2	0	0	0	0	0	3
Diabetes Mellitus	0	0	0	0	0	0	0	0	0	0	0
Acute haemorrhagic oedema of infancy	0	0	0	0	0	0	0	0	0	0	0

	2m	3m	4m	11m	14m	4yr	9yr	12yr	14yr	Other/ unknown	Total
Immune thrombo-cytopenic purpura (ITP)	0	1	0	0	1	0	0	0	0	0	2
Kawasaki's disease	0	0	0	0	0	0	0	0	0	0	0
Juvenile idiopathic arthritis	0	0	0	0	1	0	0	0	0	0	1
Dehydration	0	0	1	0	0	0	0	0	0	0	1
Death	0	0	0	0	0	0	0	0	0	0	0
Encephalitis, meningitis	0	0	0	0	1	0	0	0	1	1	3
Postural orthostatic tachycardia syndrome	0	0	0	0	0	0	0	1	0	0	1
Vaccine failure	0	0	0	0	0	0	0	0	0	0	0
Chronic fatigue	0	0	0	0	0	0	0	2	0	0	2
Venous thrombosis	0	0	0	0	0	0	0	0	0	0	0
Chronic arthritis	0	0	0	0	0	0	0	0	0	0	0
Complex regional pain syndrome (CRPS)	0	0	0	0	0	0	0	0	0	0	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 AEFI reports for all vaccines covered by the NIP. In 2018, Lareb received 1,519 reports of a total of 5,208 AEFIs (Table 5.1) [2]. Compared to 2017, the number of received reports increased by 9.8% (1,383 in 2017), while the number of reported AEFIs decreased by 4.0% (5,423 in 2017). The increase in the number of reports received can be explained by the introduction of the MenACWY vaccination in adolescents in autumn 2018. Most reported AEFIs were injection site reactions (n=1,575), fever (n=699) and crying (n=155). Of the reports, 78 (5.1%) were classified as serious.

The number of reports per dose and vaccine are mostly within the range of the last seven years (see Table 5.1). For infants aged 11 months, the number of reports has increased since 2015. An explanation for this increase is lacking. The number of reports in infants aged 14 months is also increasing. This may be explained by the replacement of Neisvac by Nimenrix last year, although the increase had already started before this change occurred. The number of reports in these infants will be closely monitored.
The decrease in the number of reports after administration of DTP-IPV at the age of 4 years that started in 2017 (n=387), continued in 2018 (n=326; see signal description below). The number of notifications received after the administration of the HPV vaccine declined further

from 257 in 2015, 146 in 2016, and 77 in 2017 to 65 in 2018. An increasing number of reports after vaccination on a different or unknown vaccination moment was observed in 2018. This was mainly observed after Infanrix hexa vaccination (n=41 vs n=21 in 2017; explanation unknown) and after vaccination with Nimenrix (n=52), where many vaccinations were given outside the NIP.

Table 5.2 summarises severe adverse events per vaccination moment as 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 AEFIs is mostly in line with previous years. The decline in reports of extensive limb swelling among 4-year-olds which was observed in 2017 (n=59) continued in 2018 (n=21).
One report of postural orthostatic tachycardia syndrome (POTS) and two reports of chronic fatigue syndrome (CFS) after HPV vaccination were received. Fatigue after HPV vaccination was reported 18 times, which is considerably less compared to 2017 (n=30).

Overall, no new signals of disturbing adverse events were found.

5.3.2 Signals

In 2018, Lareb published two signals. The first one described the increase in the number of reports per 10,000 vaccinees after administration of Infanrix-IPV® at 4 years of age since 2015. This increase mainly concerned an increase in the number of reports of injection site inflammation and fever and to a lesser extent extensive limb swelling (ELS) and other reports. Based on their data, this increase may appear to be related to differences in the vaccine administered during the primary infant infancy series. Children who were vaccinated with Infanrix hexa® in infancy were more likely to report AEFIs after administration of Infanrix-IPV® at 4 years of age than infants who received their first vaccinations with Pediacel®.
In the investigated period there was also a change in needles used. However, since the implementation of the change in needles concerned all vaccination moments of the NIP and the increase in the number of reports was limited to the number of reports after administration of the booster vaccination at 4 years of age, it is less likely that the observed increase is related to the change in needles. The researchers concluded that further research should be aimed at the possible relationship between the primary vaccination series at infant age and AEFIs after DaPT-IPV booster vaccination at 4 years of age, where the research must focus on all vaccine components.

The second signal described a sharp decrease in the number of reports after the administration of DaPT-IPV booster vaccine at 4 years of age in 2017. In that year, Infanrix-IPV® was replaced by Boostrix Polio®. The reporting rate per 10,000 vaccinated people decreased from 49.7 to 14.7. The decrease was most pronounced in the category ELS reports, where the reporting rate per 10,000 vaccinated people decreased from 10.6 to 1.0, but there was also a decrease in reporting rate in the categories of injection site inflammation, fever and other reports. The decrease in reports may be related to differences in composition of the vaccines. Vaccine comparison shows that the amount of diphtheria toxoid in Infanrix-IPV® is 15 times higher compared to Boostrix Polio®, for tetanus toxoid this is twice as high and for the pertussis

components it is a factor of 3 to 10 higher depending on the pertussis component. This finding is in line with suggestions from the literature that the level of the antigen component of the booster vaccine contributes to the occurrence in some cases of strong local reactions and ELS.

5.4 International developments

5.4.1 Non vaccine-specific adverse events

Concerns about vaccine safety can lead to decreased acceptance of vaccines and resurgence of vaccine-preventable diseases. For example, post-vaccination fever is a mild adverse event but is highly prevalent and can be accompanied by febrile convulsions, which may cause parents to delay or avoid vaccination their children. Ahn et al showed that post-vaccination fever has its own fever pattern, which is dependent on vaccine type and the presence of antipyretic drugs [3]. As such, information about post-vaccination temperature monitoring may reduce the fear of fever and can therefore lead to a reduced dropout rate.
Some other vaccine safety controversies include vaccine-induced Guillain-Barré Syndrome (GBS), vaccine-induced autoimmune diseases, and aluminium adjuvant-induced autoimmune diseases, although biological and epidemiologic evidence does not support any of these vaccine safety concerns [4-6]. The administration of an extra vaccine dose, for example due to a programmatic error, also does not show any safety issues [7].

In the next paragraphs, the safety of the vaccines included in the current NIP will be described.

5.4.2 Vaccines targeting diseases included in the current NIP

5.4.2.1 *MMR*

In 1998 Wakefield suggested that MMR vaccine causes autism. Despite the retraction of his article by the journal several years later, the hypothesised link continues to cause concern and challenge vaccine uptake. In 2019, the results of a nationwide cohort study among 657,461 children born in Denmark from 1999 through 2010 strongly supports the hypothesis that MMR vaccination does not increase the risk of autism, does not trigger autism in susceptible children, and is not associated with clustering of autism cases after vaccination [8].
In the same year, McClure found that vaccination with a measles-containing vaccine in the second year of life is associated with a similar relative risk of a first seizure in children born preterm as in those who were born full-term [9]. Another study estimated the rate and severity of AEFI recurrences and found that none of the 33 patients with seizures following MMR with/without varicella vaccine had a recurrence [10]. Overall they concluded that most patients with a history of mild of moderate AEFI can be safely reimmunised.
In a phase I/II study, no apparent differences in the incidence of AEs were found between a new MMR vaccine containing measles AIK-C, rubella Takahashi and mumps RIT4385 strains and a control group [11]. Several phase III studies showed that the safety profiles of MMR-RIT were similar to those of MMR II administered with or without other vaccines and in different age groups [12-16]. Another phase III study evaluated the reactogenicity of a MMR vaccine prepared with active pharmaceutical ingredients (API) and compared these to MMR produced by GSK [17]. Both vaccines were well tolerated, and no serious AEs had confirmed causality for the vaccine.

A case report described an adult with acute disseminated encephalomyelitis following MMR vaccination [18]. The authors recommend an assessment of vaccination safety on adult patients, and alert clinicians to ensure early diagnosis of acute disseminated encephalomyelitis. However, no other studies have been published showing this association. MMR vaccination showed to be safe and well-tolerated in children with egg allergy [19], in paediatric liver-transplant recipients [20], and in multiple myeloma patients on maintenance lenalidomide or bortezomib following autologous hematopoietic cell transplantation [21].

5.4.2.2 *Pneumococcal vaccine*

A new PCV7-TT vaccine developed by Cuba was shown in a phase I study to be safe and well tolerated [22].
No safety issues were reported with regard to PCV10 [23-25]. Public health concerns relating to previously reported adverse events in Finland were caused by concomitant changes in healthcare administration and coding [24].
For PCV13 a satisfactory reactogenicity profile was reported in infants [26], with similar safety profiles for PCV10 and PCV13 [27, 28]. In a review, Mara concluded that PCV13 in adults elicits minor local reactions. Both local and systemic adverse events are comparable to PPV23 [29-31]. Late onset of injection site reactions after PCV13 in adults is likely multifactorial, with age and the PCV13 carrier protein CRM 197 potentially associated [32].
PCV15 displayed generally comparable safety profiles or PCV13 in healthy infants [33, 34], adults [35, 36], and elderly [37].
An acceptable safety profile was found for PPV23 in healthy children, adults and elderly [38], also in elderly >=70 years of age who had received an initial vaccination at least 5 years before [39]. However, one case report was described of a young woman with ulcerative colitis under mesalazine treatment, who developed leukocytoclastic vasculitis following vaccination for PPV23, varicella and hepatitis A [40].
A phase II study in infants showed that the reactogenicity and safety of two investigational 11- and 12-valent vaccines in infants was comparable to PCV10 [41]. The reactogenicity of two investigational pneumococcal vaccines (PhD-CV/dPly vs. PHiD-CV/PhtD) co-administered with routine vaccines was comparable between the groups and did not raise concern [42].

Two reviews described that PCVs are safe for use in low-birth-weight and preterm infants [43, 44], although findings are inconsistent on the risk of apnoea [44]. Therefore, it is recommended that hospitalised extremely premature infants should be kept under observation for at least 48h after immunisation. PCVs are also shown to be safe in patients with Systemic lupus erythematosus (SLE) [45]. Concomitant administration of PCVs with Td or with influenza vaccines showed good safety profiles in adults >=50 years of age [40, 46, 47].

5.4.2.3 *Meningococcal ACWY vaccine*

As a result of the endemic increase in serogroup W disease, a vaccination moment was introduced in the Netherlands in the autumn of 2018 where the MenACWY vaccine was offered to 14-year-old adolescents. Results from a questionnaire-based study showed that adolescents reported, in particular, pain at the injection site and myalgia (Kemmeren, personal communication). Adverse events were mostly mild and transient. The frequency of systemic

events and medical care-seeking in the week after vaccination was not different than in the week before vaccination. So many of the adverse events reported may be unrelated to the vaccination. However, these events may be experienced as associated with the vaccination, which may lead to vaccine refusal. Therefore these results are important in the communication to the target group and public health providers.

The safety of MenACWY-TT vaccine was demonstrated in toddlers, although the reactogenicity after the concomitant administration of MenACWY-TT with the DTaP-IPV-HB-PRP-T vaccine was somewhat higher compared to when the vaccines were given alone [48]. The safety of this vaccine was also found for children 6 years after MenC priming [49] and in young adolescents and adults when co-administrated with Tdap and HPV2 [50]. MenACWY-D was also shown to be well tolerated with no safety concerns [51, 52]. Two reviews concluded that, although reactogenicity in some cases increased following concomitant administration, MenACWY vaccines in general and MenACWY-CRM vaccine specifically can be safely co-administered with many routinely used infant, toddler and adolescent vaccines, as well as traveller vaccines in adults [53, 54].

5.4.2.4 DTaP-IPV-HBV-Hib

Three studies, including a review, confirmed the safety of DTaP-HBV-IPV/Hib, even in co-administration with other approved vaccines although this may possibly increase reactogenicity [55-57]. A clinically acceptable safety profile was also found for Hib-MenC-TT [58]. A similar safety profile was found for a fully liquid hexavalent vaccine DTaP5-HBV-IPV-Hib compared to Infanrix-hexa [59], even when this vaccine was co-administered with MenACWY-TT conjugate vaccine in children from 12 months of age [48]. Data also support the use of a fully liquid DTaP-IPV-HBV-PRP-T hexavalent vaccine in a 2, 3, 4-month schedule without a birth dose of HBV vaccine, with a booster dose in the second year of life administered with routine childhood vaccines [60].
No safety concerns were reported for a hexavalent-pentavalent-hexavalent primary vaccination schedule followed by a pentavalent booster in co-administration with other common childhood vaccines [61]. Acceptable safety profiles were also found for DTaP [62], monovalent aP in neonates [63], DTaP-IPV/Hib in infants [64], DTaP-sIPV (i.e., a sabin-based IPV) in infants and toddlers [65], and DTaP-IPV in children aged <7 years [66]. In 2015, Canada reported a signal of large local reactions associated with vaccines recommended at the 18-months visit (DTaP-IPV-Hib-HBV and MMRV). An additional study determined whether the excess of large local reactions was caused by a specific vaccine or their co-administration in the same limb or during the same visit. The local reactions included local injection site reactions (redness, swelling, pain) reported by a health professional as meeting at least one of the following criteria: 1. Extending beyond the nearest joint, 2. Lasting >=4 days, 3. Abscess (sterile or infectious), or 4. Cellulitis treated with antibiotics. The results showed that most large local reactions were causally associated with the hexavalent vaccine and that the risk was not greater when MMRV and the hexavalent vaccine were administered in the same limb [67]. Although there is a move towards a wP prime-aP boost vaccination strategy in low- and middle-income countries, a systematic review confirmed earlier findings that, when comparing the first dose, wP is more reactogenic than aP [68]. However, Gunardi et al demonstrated the

safety of a booster dose of DTwP-HB-Hib vaccine [69]. Most AEs were mild and resolved spontaneously within three-day follow-up period.
Another systematic review concluded that both live attenuated and inactivated vaccines (using a 3-dose primary series for hexavalent and pneumococcal vaccines) are safe and well tolerated in preterm children [43]. However, apnoea represents a nonspecific stress response in preterm infants, thus the authors advised that those hospitalised at 2 months should have cardio-respiratory monitoring after their first vaccination.

In adolescents, adults and HIV-infected adults, Tdap, a new recombinant pertussis vaccine containing PTgen, an adult tetanus diphtheria [Td] vaccine, and 3 or 5 pertussis- containing components, was shown to have a well-tolerated safety profile [70-76]. The safety of DTaP-IPV was shown in pediatric healthcare workers [77]. In a meta-analysis, Xu investigated the safety of pertussis component vaccines in adolescents and adults. The results showed that these vaccines, except for a significant difference in gastrointestinal reaction (nausea, vomiting), were safe [78].

Several studies were published concerning the safety of maternal pertussis vaccination. In all these studies, no safety issues were encountered for mother and/or child [79-83]. Two reviews confirmed these results [84, 85]. Furthermore, no association was found between prenatal Tdap vaccination and an increased risk of autism spectrum disorder [86]. Thus, safety studies provide reassurance of no significant increased risk of recognised maternal conditions or of adverse events (including congenital anomalies) in infants born to vaccinated mothers.

One study assessed the effects of using needles of different sizes for administering vaccines to children and adolescents on procedural pain and other reactogenicity events [87]. It was found that using 25 mm needles for intramuscular vaccination of DTwP vaccines in the anterolateral thigh of infants probably reduces the occurrence of local reactions. The applicability of the findings to vaccines with acellular pertussis components and other vaccines with different reactogenicity profiles is uncertain. Another study compared the safety of pentavalent DTP-HBV-Hib vaccine administered by disposable-syringe jet injector to that via needle and syringe [88]. This study was terminated prematurely for precautionary reasons beyond that specified in the protocol stopping criteria, after the Data Safety Committee noted a higher frequency of injection site reactions, especially moderate and severe, in the disposable-syringe jet injector group.

5.4.2.5 *HPV*

Several studies demonstrated the safety of HPV vaccines; no correlation was found for autoimmune disorders [89], primary ovarian insufficiency [90], GBS hospitalisations [91] and diabetes mellitus type I [92]. The results of 12 years of vaccinovigilance in Italy did not identify new safety issues [93]. However, other studies did report safety issues. DeLong reported a lowered probability of pregnancy in females aged 25-29 who received a HPV vaccine [94]. However, although available, they did not adjust for one of the most important covariates that could impact pregnancy rates, i.e. adjustment for the usage of contraception. Besides that, no dose-response relationship was found for number of HPV doses and the likelihood of getting pregnant, which makes the results of this study less reliable.

In Japan, a possible association between HPV vaccination and memory impairment or involuntary movement were found in a study with 21,034 vaccinated cases and 9,245 unvaccinated controls [95], although no stratification for type of vaccine or adjustment for multiple testing had been done. In an analysis of the US VAERS, potential safety signals arose that would deserve further investigation. These included alopecia, hyperacusis, and parosmia [96]. However, due of the low rate of possible serious AEFIs, the authors concluded that the benefit-risk profile of HPV vaccines remains favourable.
A Cochrane review reported that the occurrence of severe adverse events or adverse pregnancy outcomes was not significantly higher in recipients of HPV vaccines than in women included in the control arms [97]. The methodology and conclusions of this study, however, were questioned [98-100]. The Cochrane team intends to initiate an update of the review [101].

In the discussion about the association between HPV vaccination with POTS/CFS/CRPS and symptoms including headache and orthostatic intolerance, Ward et al evaluated whether phenotypes may reflect these suspected adverse events [102]. Their results show that non-specific symptoms including headache, fatigue and dizziness feature prominently in serious AE reports. Their analysis identified a cluster of reports, likely media-stimulated, with a focus on symptoms of POTS and CFS. Another study in Denmark described a group of females reporting AE and compared them to vaccinated peers not reporting AE [103]. They found fewer cases reporting feeling sad prior to vaccination than controls (OR 0.36). This was unexpected because two recent Danish registry-based case-control studies concluded that females reporting severe AE were more likely to consult a psychologist/psychiatrist and to have pre-existing psychiatric conditions before the first HPV vaccination [104, 105]. However, recall bias may have affected the results from the recent study since this study was done in a setting where the HPV vaccine and its suspected AE were heavily debated in the media. The finding that cases to a greater extent were physically active prior to vaccination (OR 4.2) was consistent with an earlier study [104].

In a study proposal the authors presented a hypothesis that the AEFIs in a small subset of HPV vaccinees might arise from exaggerated immune system when confronted with a high dose of HPV-vlps via the non-mucosal route. The authors state that performing a study using integrated bioinformatics data is complex and needs a large sample size study based on integrated bioinformatics data analyses [106].

5.4.2.6 2vHPV, 4vHPV and 9vHPV vaccines

In a descriptive analysis of reports to VAERS, no new or unexpected safety concerns for 2vHPV were identified [107]. Furthermore, no evidence was found in the Netherlands for an increased risk of fatigue syndromes following 2vHPV vaccination [108], and in Finland no significantly increased risk was reported for associations between 2vHPV and autoimmune diseases and clinical syndromes in a nationwide retrospective register-based cohort study [109].
Results from studies on the safety of 4vHPV did not reveal new or unexpected safety concerns [110-113], even in HIV-infected girls and adolescents [114, 115]. Furthermore, no increased risk of spontaneous abortion, stillbirth, or infant mortality following unintended 4vHPV vaccination during pregnancy was found [116].

A case report was presented of myasthenia gravis following 9vHPV vaccination [117]. If this disease is reported more frequently in the future, additional research will be needed. Gilca showed that mixed HPV vaccination schedules, with one dose of 9vHPV and one dose of 2vHPV administered in different order, had an acceptable safety profile [118], although subjects who received 2vHPV as the first dose reported more local or systemic adverse events than those who received 9vHPV as the first dose. Post-second dose there were no differences in reported adverse events between the two vaccines.

Two studies demonstrated the safety of 4vHPV vaccination in males [119, 120]. The safety of HPV vaccination in males was also shown in a systematic review, although the currently available evidence on the safety of HPV vaccination in males is limited due to the small number of relevant studies [121].

5.4.2.7 *New vaccines*

The side effects of a novel Escherichia coli-produced bivalent HPV-16/18 vaccine were mild and no vaccine-related serious adverse events were noted in 7,372 women aged 18-45 years. The administration of a nonadjuvant HPV type 6 L1 VLPs vaccine to Chinese patients with recurrent respiratory papillomatosis was also well tolerated [122].

5.4.3 Other potential future target diseases

5.4.3.1 *Meningococcal B*

No safety concerns were found for 4CMenB in infants and toddlers [123-125], even in hospitalized premature infants [126], although solicited AEs were more frequent in groups receiving 4CMenB coadministered with MenACWY or 4CMenB alone than in MenACWY alone [123]. In addition, the cumulative risk of AEFIs was shown to be reduced with concomitant versus separate administration of 4CMenB and routine infant vaccines [124]. Although fever is a known adverse event after 4CMenB vaccination, no safety signal was demonstrated is these studies.

Also in adults, 4CMenB shows a good safety profile [127-129], although the frequency of fever in adults with anatomic asplenia was higher than expected (12.5%) [127], and large-scale population-based surveillance indicates frequent AEFI-associated absenteeism and medical consultations affecting the societal cost of this vaccine [128]. In adolescents and adults the recombinant protein MenB-FHbp vaccine was demonstrated to be safe as a first dose [130] and as a booster dose [131].

In two phase II studies, no safety concerns were found for the investigational MenABCWY vaccine [132, 133] although this vaccine has been shown to be reactogenic [132]. The frequency and severity of solicited reactions observed after vaccination with MenABCWY were similar to reactions observed after 4CMenB vaccination, but higher than those seen after vaccination with MenACWY.

5.4.3.2 *Varicella*

One study assessed the occurrence of SAEs during 10-year follow-up [134]. From the start to 10 years post vaccination, the rates of SAEs were similar between the vaccine groups (i.e., MMRV, MMR+V and MMR; 14.5–16.0%), and none of these were considered vaccine-related. In a

phase III trial no difference in percentages of solicited local, systemic and unsolicited adverse reactions was found between four different manufactured varicella vaccines [135], although one case report was described of a young woman with ulcerative colitis under mesalazine treatment who developed leukocytoclastic vasculitis following vaccination for PPV23, varicella and hepatitis A [40].
Several studies were published on the safety of new varicella vaccines. The safety of a varicella vaccine formulated without human serum albumin (HSA) was found to be comparable with that of the original HSA-containing vaccine in toddlers [136]. A human diploid cell SV-1 strain-based live attenuated varicella vaccine showed no significant differences in solicited adverse reactions compared with a placebo [137]. The safety and tolerability of a refrigerator-stable varicella vaccine was similar to that of the frozen formulation [138].
MMRV vaccine was well-tolerated when in either intramuscular or subcutaneous administration [139], although fewer subjects in the intramuscular group experienced injection-site AEs compared to the subcutaneous group. The rates of fever were comparable between the two groups.

5.4.3.3 *Herpes Zoster*

Many studies have demonstrated the safety of live-attenuated herpes zoster vaccination [140-143], even in combination with MMR [144] or PPV23 [145, 146]. Live-attenuated herpes zoster vaccination also appeared to be safe in patients with rheumatoid arthritis [147], *varicella zoster* virus-seropositive women [148] and HIV-infected adults [149]. Choi demonstrated the safety of a newly developed live-attenuated zoster vaccine in healthy adults aged 50 years or older in Korea [150]. No safety concerns were identified for the recently licensed recombinant zoster vaccine in immunocompetent as well as in immunocompromised people [151-157], or when co-administered with PPV23 [158]. These results correspond with four published reviews [159-162].
Six reviews evaluated both the live-attenuated vaccine and the adjuvanted recombinant vaccine [163-168]. Although both vaccines have shown promising safety, the recombinant vaccine results in higher local and systemic reactogenicity following immunisation, as anticipated with an adjuvanted vaccine

An investigational inactivated zoster vaccine was well tolerated in recipients of autologous haemopoietic stem-cell transplants [169].

5.4.3.4 *Hepatitis A*

Several studies demonstrated the safety of Hepatitis A vaccines in children aged from 12 months to adolescents, and adults [170-174], although one case report was described of a young woman with ulcerative colitis under mesalazine treatment, who developed leukocytoclastic vasculitis following vaccination for PPV23, varicella and hepatitis A [40].
In patients with a childhood-onset systemic lupus erythematosus hepatitis A vaccination showed to be safe and well tolerated [175].

5.4.3.5 *Hepatitis B*

Several studies did not find any safety concerns with regard to the simultaneous administration of HepB with hepatitis E vaccine in adults [176], with EV71 and MenA in infants [177], in adolescents previously vaccinated with DTPa-HBV-IPV/Hib [178], and in patients with rheumatoid arthritis [179]. Furthermore, no increased risk for adverse events was observed among pregnant women who received maternal HepB or their offspring [180]. Results from clinical trials showed that Heplisav-B compared favourably with Engerix-B in terms of its safety profile [181], and the new HBAI20 vaccine seems safe and well-tolerated as well [182]. Burny studied the safety of AS01B- and Alum-adjuvanted vaccines. Local and systemic symptoms were more frequent in individuals who received HBsAg-AS01B than after HBsAg-Alum, but these were mild and short-lived [183].
Geier et al suggest that thimerosal-containing hepatitis B vaccines administered within the first six months of life increase the risk of premature puberty [184]. However, over the years the research methodology of these authors has been criticised several times [185](http://www.vaccinesafety.edu/Vaccines_Do_Not_Cause_Autism.htm). The reliability of their study results is therefore questionable. In the Netherlands, thimerosal is not used as a preservative in routinely recommended childhood vaccines.
Mouchet et al assessed the robustness of the link between HepB vaccination and central demyelination by analysing all validated cases reported in 1980-2000 and conducting observed-to-expected comparisons [186]. They found that the number of reported cases sometimes approached the expected number irrespective of underreporting. So their results were not consistent for a strong association and they stated that the current recommendations should remain the preferred strategy.

One study compared the safety of intramuscular vs. intradermal delivery of a hepatitis B booster vaccination in healthy subjects [187]. Local adverse events were reported more frequently for intradermal compared to intramuscular administration. However, overall the authors concluded that the investigated intradermal injection device proved to be a good method to offer intradermal vaccination.

5.4.3.6 *Rotavirus*

Several studies showed the favourable benefit-risk balance for Rotarix [188-190]. Haber et al studied the possible association between Rotarix and lower respiratory tract infections [191], but no significant difference in LRTI reports to VAERS was found. Two studies concluded that rotavirus vaccination is associated with a reduced incidence of type I diabetes [192, 193]. Hemming-Harlo showed that RotaTeq did not alter the occurrence of diabetes mellitus type I but decreased the prevalence of celiac disease in childhood and adolescence [194]. They proposed that wild-type rotavirus may trigger celiac disease and the triggering effect can be prevented or reduced by rotavirus vaccination. Data from US new-borns from a commercial insurance did not find an increased risk of intussusception or other adverse events following vaccination with RV, except potentially for a small increased risk of otitis media, particularly in Rotarix [195]. Other reviews also concluded that data support the safety of rotavirus vaccines [196, 197].
New vaccines such as Rotavac, RotaSill and RotaSill-Liquid were shown to be well tolerated [198-202].

5.5 Literature

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*RIVM publication

6
NIP-wide research topics

J. Hoes, T.M. Schurink-van 't Klooster, M.J. Knol

6.1 Key points

- There are no major gender differences in protection due to differences in IgG level for the studied pathogens in the Netherlands. If differences were observed, girls were favoured over boys.

6.2 Gender-specific effects of vaccination

As part of the RIVM's strategic programme (SPR), gender-specific effects of vaccination were investigated. As infectious diseases can differ by sex in their incidence, prevalence, or severity of disease due to differential sex hormones or sex-dependent immune responses [1, 2], we aimed to assess possible sex differences in immunoglobulin levels (IgG) after infant and childhood vaccination [3].
Hence, data from PIENTER2, the second national cross-sectional serosurvey, which was conducted in 2006/2007, were used [4]. We compared IgG levels against measles, mumps, rubella, diphtheria, tetanus, poliomyelitis, pertussis, *Haemophilus influenzae* type b (Hib), and Meningococcal serogroup C (MenC) between girls and boys both short-term (1 month to 1 year) and longer-term (1 to 3 years) after infant and childhood vaccinations, and the proportion of children reaching a protective IgG level.
We did observe some differences in IgG at specific time points after vaccination, for example against measles, mumps, rubella, MenC, and polio. The geometric mean concentration or titre (GMC/T) girls:boys ratios ranged between 1.10 for polio type 1 <1 year after the first childhood booster to 1.90 for MenC <1 year after infant vaccination, indicating higher antibody levels in girls. Proportions with protective levels differed at 1-3 years after infant vaccination for mumps (82.5% boys vs. 91.9% girls, p=0.046), and at the same time point for MenC (7.0% boys vs. 18.2% girls, p=0.015), and polio type 1 (87.8% boys vs. 95.9% girls, p=0.047).
Overall, differences in IgG between boys and girls were generally small and not consistent, neither between pathogens nor within pathogens. If differences were observed, girls were favoured over boys, as has been shown before [5, 6]. On the whole, the results suggest that there are no major sex differences in protection resulting from IgG-level differences for the studied pathogens in the Netherlands. This is a reassuring message as boys and girls are currently eligible for the same vaccinations under the NIP.

6.3 Protection among premature children

The current NIP might provide insufficient protection for premature children given their immature immune system. Currently, approximately 15,000 premature babies per year are born in the Netherlands. In a prospective observational study (PRIEMA study) 296 premature children were recruited, distributed over three gestational age groups (<28, 28-32 and 32-36 weeks). Their 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 six weeks (pre-vaccination), at five months (post-primary series), and at 12 months (post-booster). After the primary series, only 40% of the premature children had sufficient protection against Hib (≥ 0.15 µg/ml), which increased up to 88% after the booster at 11 months. Protection against diphtheria, tetanus and pertussis was sufficient after both the primary series and the booster. From the ten pneumococcal serotypes, four (serotype 4, 6B, 18C and 23F) showed a relatively low percentage of protection after the primary series varying between 45 and 75%, but this increased to sufficient protection (>95%) after the booster. No real differences in the proportion of protected children were observed between the three gestational age groups; the GMCs in the premature groups were a bit lower compared to the term control group both after the primary series and the booster. After the implementation of maternal pertussis vaccination, the Dutch primary vaccination schedule for DTaP-IPV-Hib-HepB and pneumococcal vaccination will be changed from a 2-3-4 schedule to a 3-5 schedule. For premature children, however, a 2-3-5 schedule will be implemented.

6.4 Literature

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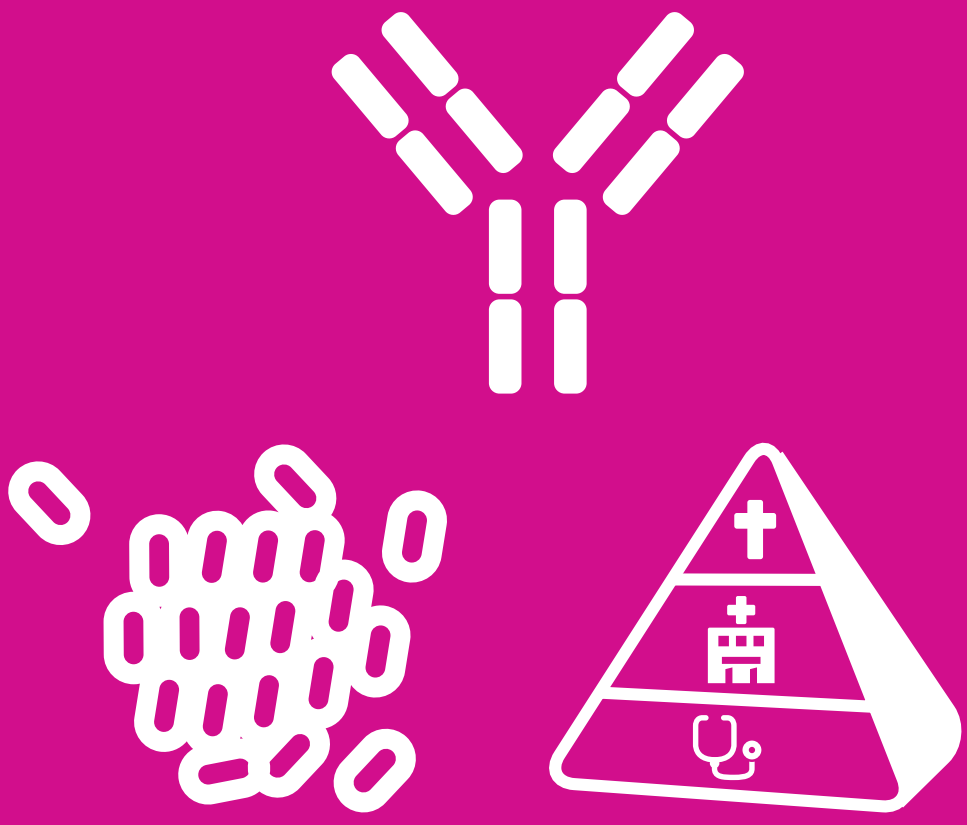
*RIVM publication

7
Current National Immunisation Programme



7.1 Diphtheria

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

7.1.1 Key points

- In 2018, two diphtheria cases were reported.
- In 2019, up to 1 July, no diphtheria cases were reported.

7.1.2 Tables and figures

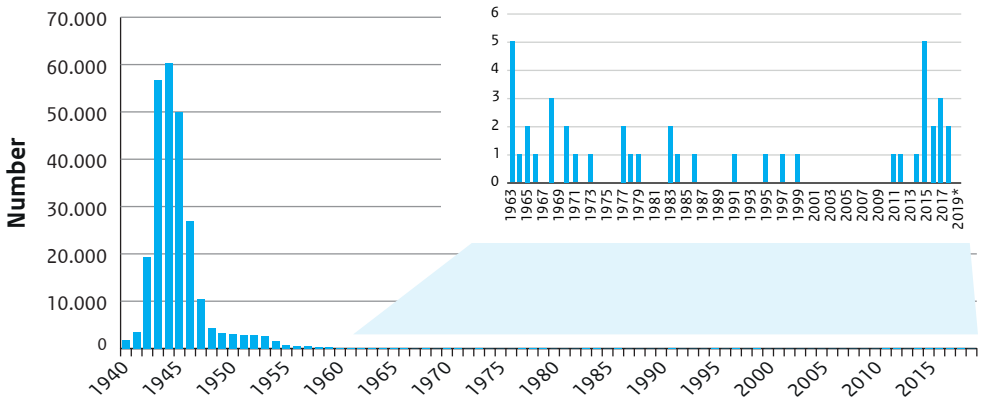


Figure 7.1.1 Diphtheria notifications per year for 1940-1962 (left) and 1963-2019*(right)

*notifications up to July 2019 are included

Table 7.1.1 Laboratory results of confirmation testing of *Corynebacterium diphtheriae* and C. *ulcerans* at RIVM for 2016-2019*. Date of delivery to the laboratory 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
2016	12	1	1	N/A	2	1	N/A	1
2017	9	1	0	0	0	2	N/A	2
2018	7	0	N/A	N/A	1	2	1	1
2019*	1	0	N/A	N/A	4	0	N/A	N/A

*Up to 1 July 2019
N/A= not applicable

7.1.3 Epidemiology

In 2018, two notifications of diphtheria were received (Figure 7.1.1). Both concerned cutaneous diphtheria infections caused by *C. Ulcerans*. Cases were male, born in 1966 and 1959. Both were vaccinated with three or more doses. The cause of infection remains unclear in both cases as symptoms were present long before the cases were reported. In 2019, up to 1 July, no cases of diphtheria were reported.

7.1.4 Pathogen

In 2018, the RIVM received ten *C. diphtheria* or *C. ulcerans* strains, all from cutaneous samples. Two strains (which correspond to the two notifications mentioned above) were PCR-positive. Only PCR-positive cases are tested for toxin production with the Elek test. One of these samples was Elek positive, meaning that toxin was produced. The other had a non-conclusive Elek result. In 2019 up to 1 July, the RIVM received five *C. diphtheria* or *C. ulcerans* strains, but none were PCR-positive.
See table 7.1.1 for details on laboratory results for the respective strains.

7.1.5 International developments

In 2018, three countries in the Region of the Americas (Colombia, Haiti and the Bolivarian Republic of Venezuela) continued to report confirmed diphtheria cases due to low vaccination coverage [1]. The outbreak continued in Haiti and Venezuela in 2019 [1].
The Dutch Leeward Antilles (Aruba, Bonaire and Curacao) are located close to the northern coast of Venezuela, and numerous Venezuelan refugees come to these islands because of their proximity. Considering the small size and limited capacity of the islands, this large influx of refugees introduces a risk of diphtheria being introduced on the islands. Additionally, a study

performed on the islands showed that immunity against diphtheria is suboptimal for residents aged over 30 years [2]. Health authorities on the Dutch Leeward Antilles should be actively trying to detect early cases in order to prevent subsequent transmission.
In addition, Yemen and Bangladesh experienced a diphtheria outbreak in 2018 due to the humanitarian crisis and low vaccination coverage in the governorates and refugee camps [3, 4]. Children are affected most. At the beginning of 2019, the weekly number of probable diphtheria cases stabilised in Yemen [5]. In Bangladesh, the outbreak is still ongoing [6].
In 2019, a thorough review of the global diphtheria epidemiology was published. This review showed that the protection of young children (<15 years) increased as the DTP vaccination coverage increased. In countries with higher case counts, the cases mostly occurred in unvaccinated and older children, which is consistent with the waning vaccine immunity. To further decrease the diphtheria incidence, implementing booster doses and attaining a high vaccination coverage of DTP are essential [7].

7.1.6 Literature

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*RIVM publication

7.2 *Haemophilus influenzae* disease

M.J. Knol, A. van der Ende, W. Freudenburg, G. Berbers, T. Bosch, H.E. de Melker

7.2.1 Key points

- In 2018, the number of cases of *Haemophilus influenzae* type b (Hib) disease was similar to 2017 (43 vs 46 cases).
- In 2018, the incidence of Hib disease was highest among children under 5 years old (2.1 per 100,000). The increasing trend in incidence observed from 2011 to 2016 ceased in 2017 and 2018.
- There were 11 vaccinated Hib cases (55% of vaccine-eligible Hib cases) in 2018, resulting in a Hib vaccine effectiveness estimate of 91%, similar to previous years.
- In 2018, more cases of non-typeable Hi (NTHi) disease were reported than in 2017 (167 vs. 159), confirming a continuing increase in NTHi disease.
- No rise was observed in Hi due to other serotypes.

7.2.2 Figures

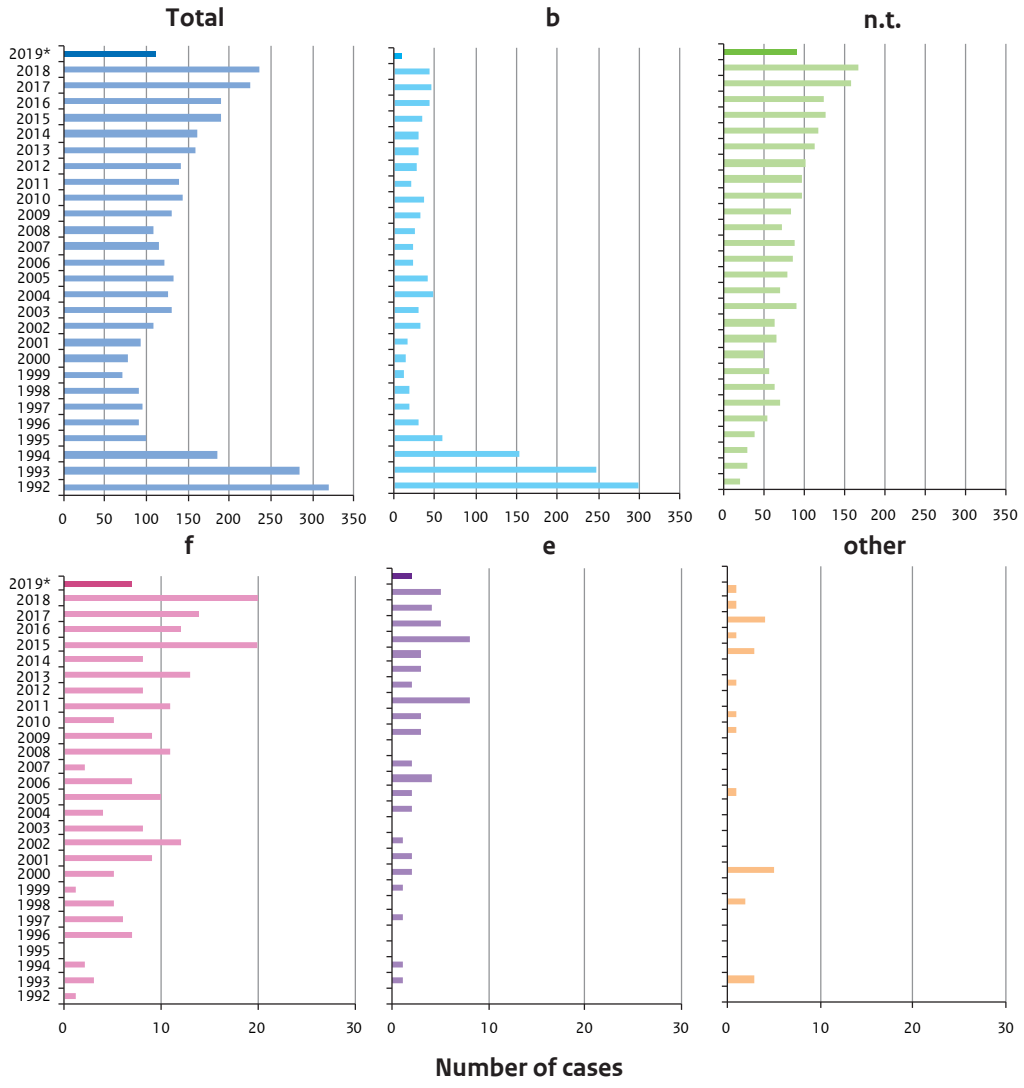

Figure 7.2.1 Number of *Haemophilus influenzae* cases per serotype, 1992-2019* (*up to May)

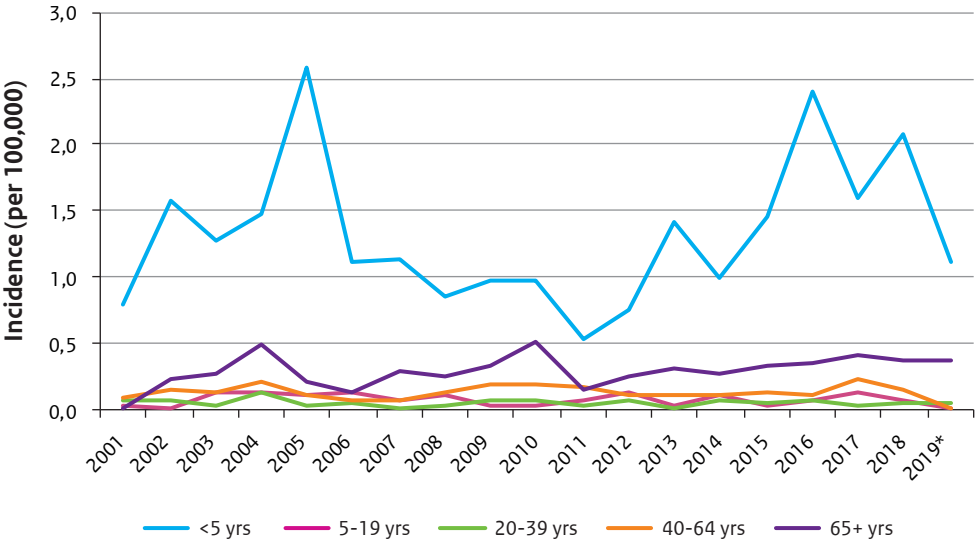

Figure 7.2.2 Age-specific incidence of *Haemophilus influenzae* type b (Hib) disease, 2001-2019* (*up to May)

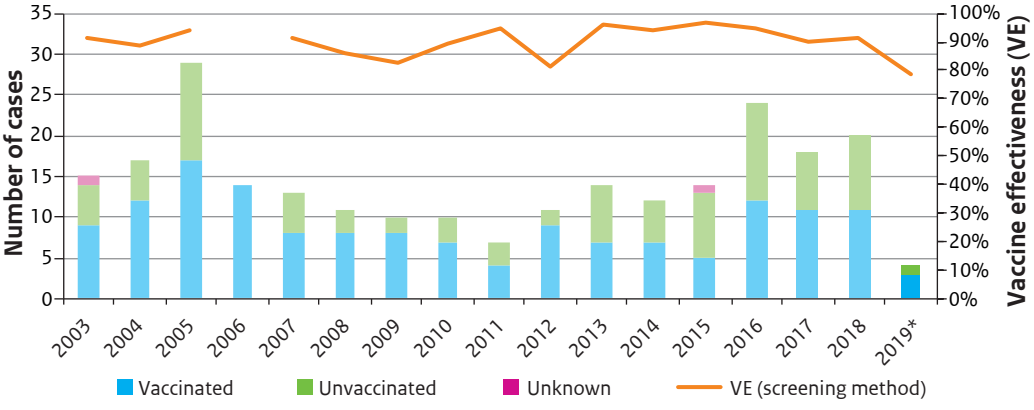

Figure 7.2.3 Number of *Haemophilus influenzae* type b (Hib) cases in cohorts eligible for vaccination (i.e. born after 1 April 1993) by vaccination status and estimated vaccine effectiveness, 2003-2019* (*up to May)

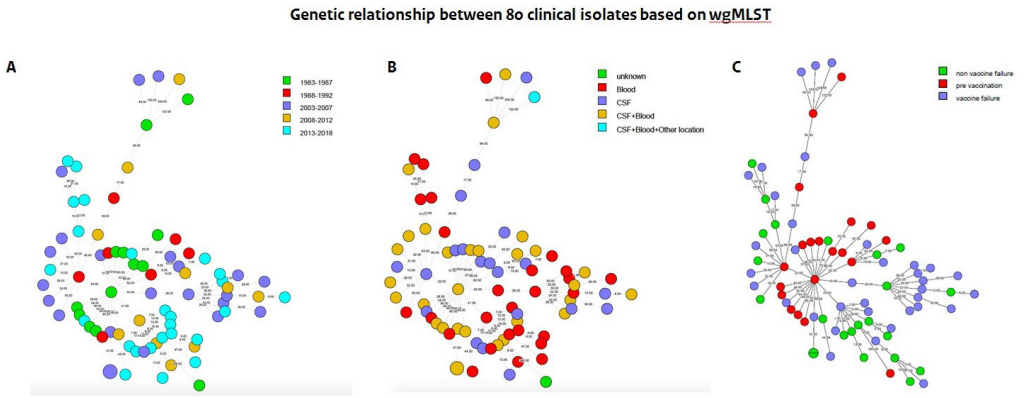

Figure 7.2.4. Genetic relationship between 80 clinical isolates based on wgMLST. In this figure, the minimum spanning tree of all 80 *Haemophilus influenzae* type b (Hib) clinical isolates that have been sequenced are depicted. Each node in this spanning tree based on wgMLST represents a single Hib isolate. The length of the lines between isolates represents the number of different genes. No clustering of strains by year of isolation (A), invasiveness (B), or vaccination status (C) can be observed.

7.2.3 Epidemiology

7.2.3.1 Hib disease

7.2.3.1.1 Incidence

Between 2011 and 2016, the number of Hib cases rose from 22 to 44. In 2018, the number of Hib cases amounted to 43 (incidence: 0.25 per 100,000), similar to 2017 (n=46) and 2016 (n=44), so no further increase was observed (Figure 7.2.1). The incidence was highest in children <5 years old (2.1 per 100,000; n=18) (Figure 7.2.2), however it did not rise any further in this age group after 2016. Up to May 2019, ten Hib cases have been reported, somewhat less than in the same period in 2018 (n=17).
The outcome status was known for 29 and nine cases in 2018 and 2019, respectively. Of these, one patient, a baby too young to be vaccinated, died in 2018.

7.2.3.1.2 Vaccinated cases

In 2018 and 2019 (up to May), 20 and four Hib cases were reported among cohorts eligible for vaccination, respectively (Figure 7.2.3). Nine (38%) of these cases were unvaccinated (8eight in 2018, one in 2019), one case was vaccinated once (in 2018) and 14 (58%) were sufficiently vaccinated (i.e. received at least two vaccinations with at least two weeks between the second vaccination and date of diagnosis; 11 in 2018 and three in 2019). The unvaccinated children were between seven and 22 months old. Most vaccinated cases (n=9 in 2018 and n=3 in 2019) were younger than five years old. Information on underlying disease was available for 13 of the 14 vaccinated cases. One of these cases (8%) had a known immune disorder.

7.2.3.1.3 Vaccine effectiveness

The estimated vaccine effectiveness (VE) of Hib vaccination using the 'screening method' was 91% (95%CI 79-96%) in 2018 (Figure 7.2.3). The overall VE for 2003-2019 was 91% (95%CI 89-93%).

7.2.3.2 Non-typeable Hi (NTHi) disease

In 2018, 167 cases of NTHi were reported. This was more than in 2017 (159 cases), confirming a continuing rise in NTHi disease (Figure 7.2.1). Up to May 2019, 90 cases have been reported, which is similar to the number reported in the same period in 2018 (91 cases). In 2018, the incidence was still highest among persons aged 65 and over (2.9 per 100,000; n=94) and children aged under five years old (1.8 per 100,000; n=16). This increasing trend is also seen in other European countries [1]; there is no clear reason for this increase.

7.2.3.3 Disease due to other Hi serotypes

In 2018, five Hi cases with serotype e (Hie) were reported, similar to previous years (Figure 7.2.1). Up to May 2019, two Hie cases have been reported. In 2018, 20 cases of Hif were reported, which is slightly more than in previous years (Figure 7.2.1). Up to May 2019, seven Hif cases have been reported. In 2018 and 2019 (up to May), one Hi case with serotype a has been reported (Figure 7.2.1).

7.2.4 Pathogen

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

7.2.5 Current/ongoing research at RIVM

Because of the increase in the number of Hib cases from 2011 to 2016, genotypic characterisation of disease isolates was performed by whole genome sequencing to examine genetic differences over time and changes induced by vaccination pressure. A total of 80 Hib strains isolated from children <5 years of age diagnosed with invasive Hib disease were obtained from the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM). Twenty strains were randomly selected from the pre-vaccine era (1986-1992) and 60 strains, from both vaccinated and unvaccinated children, represented the vaccine era (2003-2018). Complete genome sequences are only available in the public domain for a limited number of Hib strains. Therefore, three recently isolated Dutch strains were selected for full genome annotation to serve as reference genome. For two strains, a circular chromosomal sequence was obtained using a hybrid approach combining both long-read sequencing on the MiniON (Oxford Nanopore Sequencing) and short-read next-generation-sequencing (Illumina platform). These new reference genomes will be deposited in BioProject upon acceptance of the manuscript for publication. We constructed a whole-genome multi-locus sequence-type (wgMLST) scheme on the newly built reference genome. Next, wgMLST was used to infer genetic relationships between the 80 Hib isolates that were subject to WGS. A minimum spanning tree (MST) based on wgMLST showed substantial variation within the Dutch Hib population, with an average distance of 35 genes between two neighbouring isolates (range 1-150 genes). There was no apparent clustering in the wgMLST by year of diagnosis (Figure 7.2.4A), invasiveness (Figure 7.2.4B), or vaccination status (Figure 7.2.4C). However, the isolates from the pre-vaccination era seem to cluster closer to each other than isolates after the introduction of the vaccine. The preliminary data suggest that the recent increase in cases is not caused by clonal expansion of a more successful and possibly vaccine-evasive strain.

7.2.6 International developments

Soeters et al described trends in invasive Hi disease in the United States in the period 2009-2015 [2]. During 2009-2015, the annual incidence of Hi disease was 1.70 cases per 100,000. Non-typeable Hi had the highest incidence (1.22) as compared to Hib (0.03; 4%) and non-b encapsulated serotypes (0.45). Of non-b encapsulated serotypes, serotype f was most prevalent. Compared to 2002-2008, the incidence of invasive Hi disease increased by 16% driven by increases in serotype a disease and non-typeable Hi disease.

In a recent report, Deghmane et al described the epidemiology of Hib in France and compared microbiological characteristics of invasive and non-invasive Hib isolates using whole genome sequencing [3]. A significantly higher proportion of beta lactamase-negative ampicillin-resistant (BLNAR) isolates was observed among non-invasive isolates (24% versus 7%, $p<0.001$). Analysis of the ftsI gene, which encodes PBP3, showed phylogenetic clustering into four groups suggesting a cumulative effect of mutations on beta lactam resistance. The authors postulate that these PBP modifications lead to biological cost, explaining the higher proportion of BLNAR in non-invasive isolates.

7.2.7 Literature

1. Whittaker R, Economopoulou A, Dias JG, Bancroft E, Ramliden M, Celentano LP. Epidemiology of Invasive *Haemophilus influenzae* Disease, Europe, 2007-2014. Emerging infectious diseases. 2017;23(3):396-404.
2. Soeters HM, Blain A, Pondo T, Doman B, Farley MM, Harrison LH, et al. Current Epidemiology and Trends in Invasive *Haemophilus influenzae* Disease-United States, 2009-2015. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2018;67(6):881-9.
3. Deghmane AE, Hong E, Chehboub S, Terrade A, Falguieres M, Sort M, et al. High diversity of invasive *Haemophilus influenzae* isolates in France and the emergence of resistance to third generation cephalosporins by alteration of ftsI gene. The Journal of infection. 2019;79(1):7-14.

7.3 Hepatitis B

I.K. Veldhuijzen, M. Visser, F.M. van Heiningen, B.H.B. van Benthem, J. Cremer, K.S.M. Benschop, A.J. King, H.E. de Melker

7.3.1 Key points

- Of the 1153 reported hepatitis B cases in all, 9% have an acute infection and 89% a chronic infection.
- The incidence of reported acute hepatitis B cases remained stable in 2018 at 0.6 per 100,000 population.
- Among both men and women, heterosexual contact was the most frequently reported risk factor for acute HBV infection.
- In 2018, genotype A continued to be the dominant genotype among acute HBV cases with 63% of 63 genotyped cases, followed by genotype D (16%).
- After a rise in 2017, the number of newly diagnosed chronic HBV infections dropped to 1030 in 2018, corresponding to an incidence of 6.5 per 100,000 population.
- Ninety 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.
- No cases of acute hepatitis B were reported among children born after the introduction of universal HBV vaccination in 2011.

7.3.2 Tables and figures

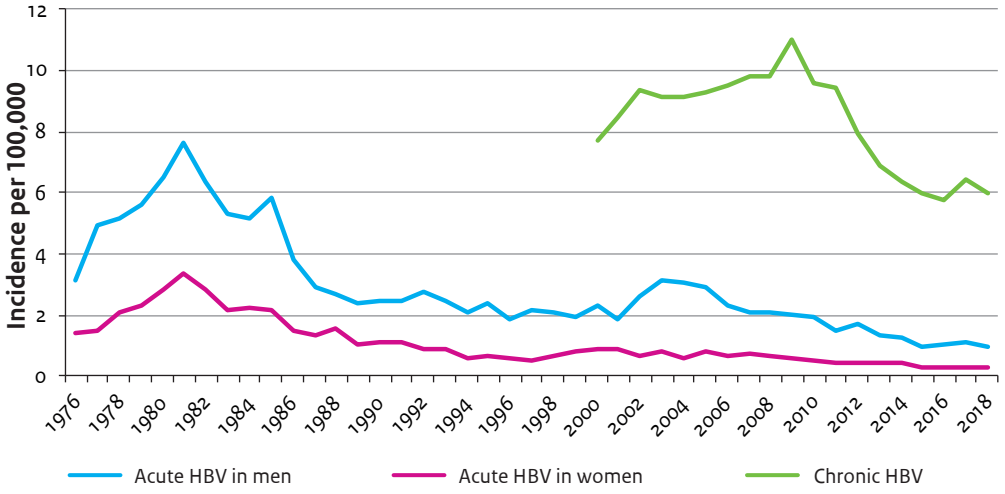

Figure 7.3.1 Incidence of acute HBV infections in men and women in the Netherlands from 1976 and chronic HBV infections from 2000
Source: Osiris

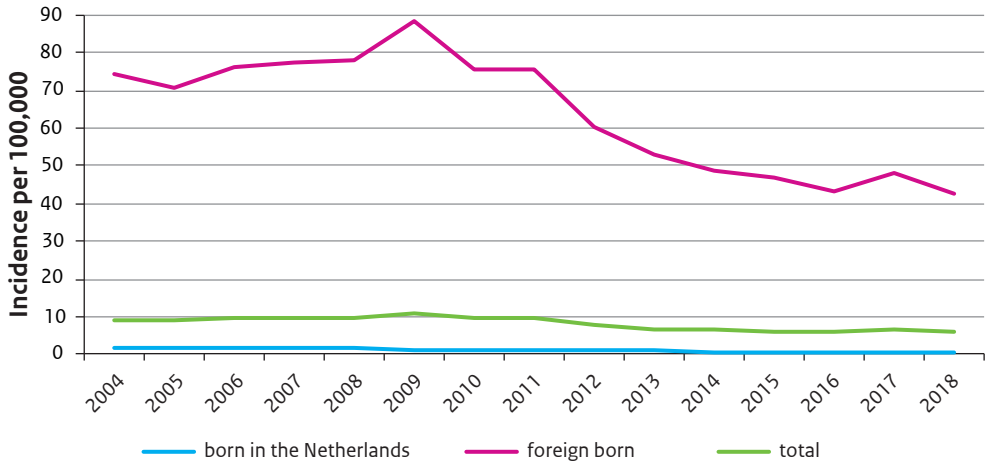

Figure 7.3.2 Incidence of chronic HBV infections in the Netherlands between 2004 and 2018 by country of birth
Source: Osiris

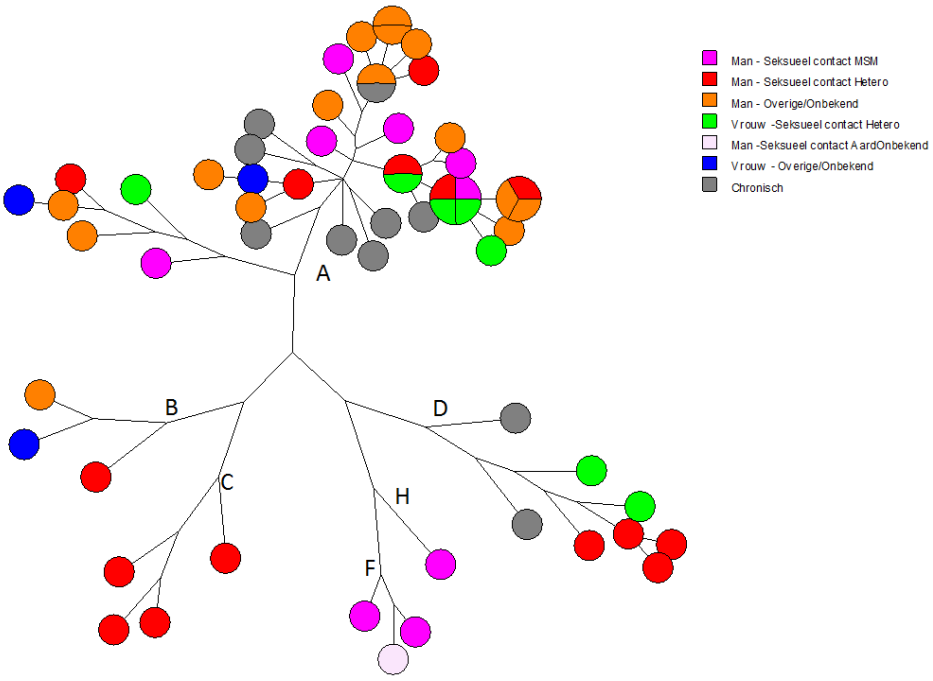

Figure 7.3.3 Optimised maximum parsimony tree based on the full length sequence of HBV cases in the Netherlands in 2018 by reported transmission route (n=60)
gX: genotype

7.3.3 Epidemiology

In 2018, 1153 cases of hepatitis B virus (HBV) infection were notified. Of these, 1030 (89%) were chronic infections and 104 (9%) acute infections (19 cases unknown status).

7.3.3.1 Acute HBV epidemiology

The number of acute HBV infections reported in 2018 (104 cases) was lower than in 2017 (115 cases). In the first half of 2019, 33 cases of acute HBV with disease onset in 2019 were reported. The incidence of acute HBV notifications in 2018 was 0.6 per 100,000 population, 1.0/100,000 among men and 0.2/100,000 among women. The HBV incidence seems to have stabilised since 2015 after having declined for both men and women since 2004 (Figure 7.3.1). After a gradual increase from around 32 years in the early nineties to 45.9 years in 2016, the mean age at infection has decreased in 2017 and 2018. In 2018, the mean age of patients with acute HBV infection was 43.6 years and is higher in men (45.2) than in women (37.3). No cases of acute hepatitis B were reported among children born after the introduction of universal HBV vaccination in 2011; the youngest patient was 18 years old.

In 2018, most cases of acute HBV infection (59%) were acquired through sexual contact. For 32% of the reports of acute HBV infection, the most likely route of transmission remained unknown despite source tracing. The proportion with unknown transmission route is higher compared to the previous year (15%). Among men (83 cases), sexual contacts between MSM accounted for 19% of acute infections, with heterosexual transmission accounting for 24%. Among women (21 cases), heterosexual contact accounted for 67% of cases. The majority of patients with acute hepatitis B were born in the Netherlands (74%).

7.3.3.2 *Chronic HBV epidemiology*

After an increase in the number of chronic HBV notifications in 2017, the number of cases decreased to 1030 in 2018 (incidence 6.0 per 100,000, compared to 6.5 per 100,000 in 2017) (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 2018, 90% of the chronic HBV patients for whom the country of birth was known, were born abroad. The incidence of chronic hepatitis B in people born abroad is about 70 times higher than that of people born in the Netherlands (43 compared to 0.6 per 100,000 population (Figure 7.3.2). The number of notifications per country of birth fluctuates over time. In 2018, the most frequently reported countries of birth were China (n=104, 10%), Turkey (n=88, 9%), Eritrea (n=62, 6%), and Syria (n=52, 5%). Half of the cases acquired chronic HBV infection through vertical transmission. In around one third (37%) of reports of chronic HBV infection, the most likely route of transmission was unknown. Sexual contact was the source of infection of 4%, and for the remaining 9%, 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 for genotyping are collected from all acute HBV infections and from chronic infections in MSM and in people detected through the vaccination programme for behavioural risk groups. In 2018, samples were available for molecular typing of 63 acute HBV cases (61%) and 10 chronic HBV cases (1%). PCR amplification and sequencing gave results for 60 samples of HBV infections for the full-length genome. An optimised maximum parsimony tree of these sequences by the most likely transmission route is shown in Figure 7.3.3. In the Netherlands, seven different genotypes were found (Genotype A-F, H). Genotype H was seen for the first time in two men with acute HBV from two different GGD regions. One case got infected though MSM contact and the transmission route remained unknown for the other. 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, 56% were genotype A followed by 16% genotype D. Genotype A was also most common among chronic cases in risk groups (6/10; 60%), followed by genotype D (2/10; 20%).

7.3.5 Research

The updated chronic hepatitis B and C prevalence in the Netherlands and the results of a cost-effectiveness analysis of screening for these infections among migrants that have been described in earlier NIP reports, have now also been published [1, 2]. The estimated prevalence of chronic HBV infection in the general population is 0.34%, and screening is shown to be cost-effective for migrants from countries with a chronic HBV prevalence of ≥0.41%.

7.3.5.1 Perinatal transmission of hepatitis B virus

The progress in the Netherlands towards triple elimination of mother-to-child transmission of HIV, syphilis and hepatitis B has been evaluated based on data for the period 2009-2015 [3]. In 2014 and 2015, more than 99% of children born to mothers with a chronic HBV infection received hepatitis B immune globuline (HBIg) and a birth dose of vaccine. After 2012, no cases of chronic HBV infection have been reported in children less than two years of age.

7.3.5.2 Predictors of hepatitis B vaccination completion among people who use drugs

Data from the hepatitis B vaccination programme for risk groups were analysed for the target group of people who use drugs (PWUD) in the period 2002-2011. In this period, 18,000 PWUD were reached, 15,750 of whom were eligible for vaccination. Of those, 58% completed a series of three HBV vaccinations. Factors associated with a higher completion rate were: starting vaccination in the earlier years of the program, older age, intravenous drug use, vaccine administration by addiction care centres, and flexibility in location of vaccine delivery [4].

7.3.5.3 Prevalence and awareness of chronic HBV among first-generation migrants

A study among the general population from different countries of birth in Amsterdam found that the age- and gender-adjusted chronic HBV prevalence was highest among Ghanaian participants (5.4%), followed by Turkish (4.1%), African-Surinamese (1.9%), Moroccan (1.2%), South-Asian Surinamese (0.9%), and Dutch (0.4%) participants [5]. Over 40% of the participants were unaware of their chronic HBV infection, which emphasises the need for screening of these migrant groups.

7.3.6 International developments

The impact of hepatitis B vaccination on the epidemiology of acute hepatitis B virus infections in Europe has been described based on data reported to the ECDC [6]. The incidence of acute HBV notifications in EU/EEA countries decreased from 1.6 per 100,000 population in 2006 to 0.7 in 2014. Significant decreasing trends were observed in countries with universal HBV vaccination before 1995, a catch-up strategy, and a vaccine coverage >=95%. Bulgaria and Latvia reported the highest notification rates of acute HBV infection, but also showed a marked decrease over time.

7.3.7 Literature

1.* Koopsen J, van Steenbergen JE, Richardus JH, Prins M, Op de Coul ELM, Croes EA, et al. Chronic hepatitis B and C infections in the Netherlands: estimated prevalence in risk groups and the general population. Epidemiol Infect. 2019;147:e147.

2.* Suijkerbuijk AWM, van Hoek AJ, Koopsen J, de Man RA, Mangen MJ, de Melker HE, et al. Cost-effectiveness of screening for chronic hepatitis B and C among migrant populations in a low endemic country. PLoS One. 2018;13(11):e0207037.

3.* Visser M, van der Ploeg CPB, Smit C, Hukkelhoven C, Abbink F, van Benthem BHB, et al. Evaluating progress towards triple elimination of mother-to-child transmission of HIV, syphilis and hepatitis B in the Netherlands. BMC Public Health. 2019;19(1):353.

4.* Raven S, Urbanus A, de Gee A, Hoebe C, van Steenbergen J. Predictors of hepatitis B vaccination completion among people who use drugs participating in a national program of targeted vaccination. Vaccine. 2018;36(35):5282-7.

5. Zuure FR, Bil J, Visser M, Snijder M, Boyd A, Blom P, et al. Hepatitis B and C screening needs among different ethnic groups: A population-based study in Amsterdam, the Netherlands. JHEP Reports. 2019;*https://doi.org/10.1016/j.jhepr.2019.04.003*.

6. Miglietta A, Quinten C, Lopalco PL, Duffell E. Impact of hepatitis B vaccination on acute hepatitis B epidemiology in European Union/European Economic Area countries, 2006 to 2014. Euro Surveill. 2018;23(6).

* 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, K. van Eer, 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

- The Ministry of Health, Welfare and Sport decided to offer HPV vaccination to boys in addition to girls as was recommended in June 2019 by the Health Council of the Netherlands. It was recommended that vaccination should be provided close to the age of nine years. In addition, they are also looking into the options for offering unvaccinated boys and girls the vaccination up to 26 years of age.
- In a prospective cohort study (HAVANA), high vaccine effectiveness (VE) of 95.3% against vaccine types HPV16/18 was found for persistent cervicovaginal infections up to eight years post vaccination. In addition, significant cross-protection of 81.5% against persistent HPV infections by HPV31/45 was observed.
- Using data from the PASSYON study, a high VE against anal HPV16/18 infection of 89.9% was calculated. This was comparable to the VE against cervicovaginal HPV16/18. In addition, significant cross-protection against anal HPV45 (100%) and HPV31 (73%) was found.

7.4.2 Tables and figures

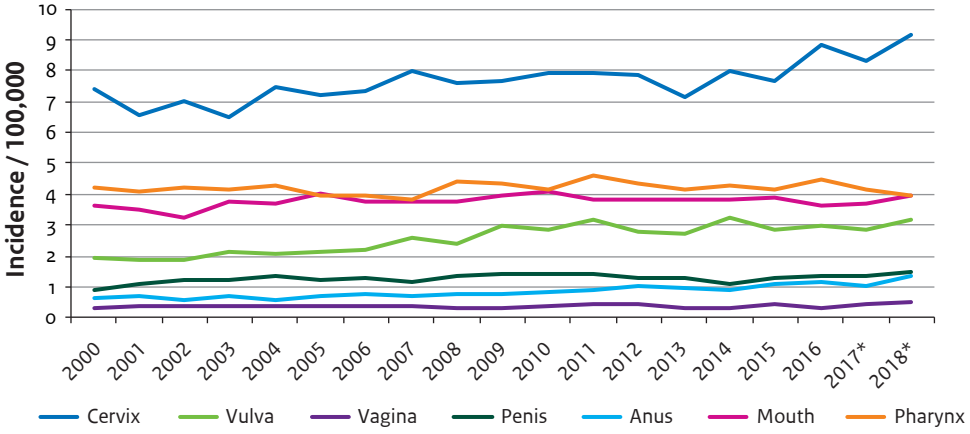

Figure 7.4.1 Incidence / 100,000 (standardised by the European standardised rate) of new cervical, anogenital, mouth/oral and pharynx/pharyngeal cancer cases in the Netherlands in the 2000-2018 period, by cancer type

* Preliminary figures

Source: the Netherlands Cancer Registry (NKR)

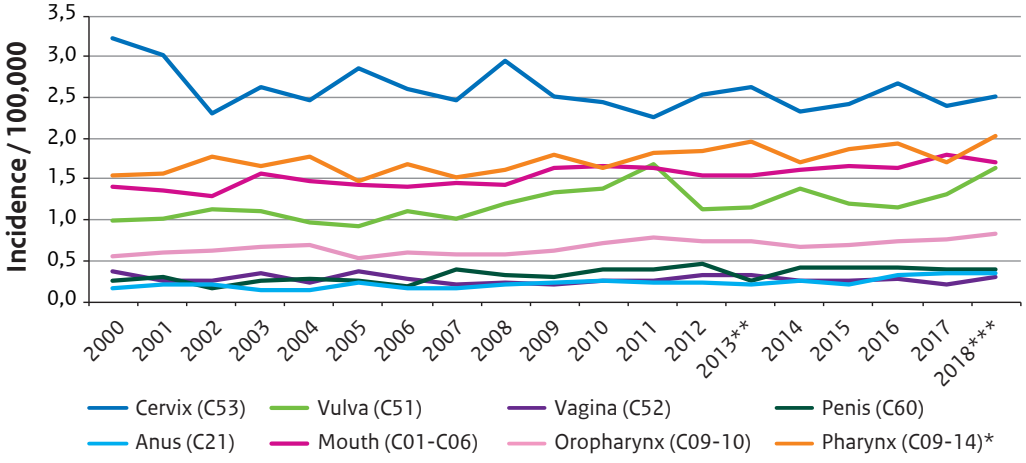

Figure 7.4.2 Incidence / 100,000 of deaths related to cervical, anogenital, mouth, oropharynx and pharynx cancer cases in the Netherlands in the period 2000-2018, by cancer type

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

** In 2013, CBS started to use international software for automatic coding of causes of death, making the statistics more reproducible and internationally comparable. Due to this change, some significant shifts in causes of death have been observed.

*** Preliminary figures.

Source: CBS

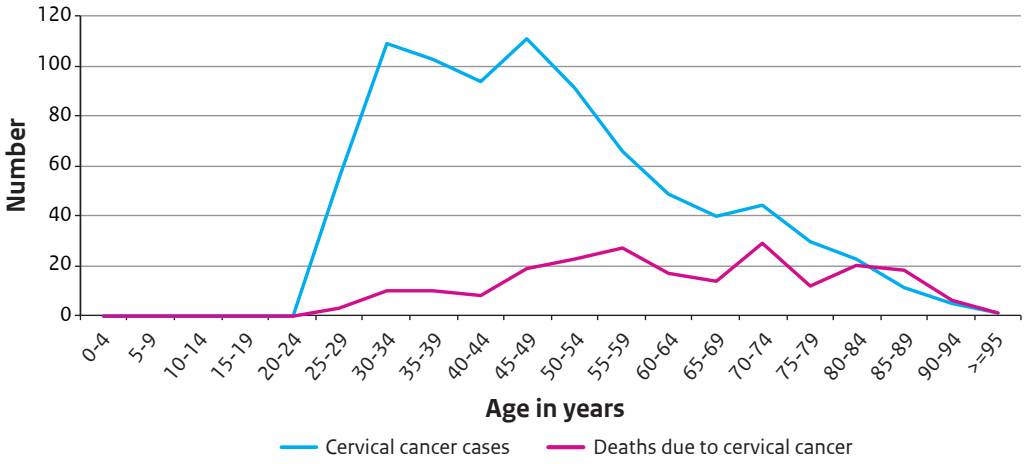

Figure 7.4.3 Age-specific number of cervical cancer cases and deaths due to cervical cancer in the Netherlands in 2018*

* Preliminary data

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

Incident infections	Adjusted* VE (95% CI)
Vaccine types (HPV16/18)	77.7% (67.0-85.0%)
Cross-protective types (HPV31/45)	70.5% (54.5-80.8%)
Cross-protective types (HPV31/33/45)	56.4% (39.2-68.7%)
Vaccine and cross-protectives types (HPV16/18/31/45)	70.9% (60.8-78.3%)
hrHPV types	12.8% (00.8-23.4%)
Types 9-valent vaccine (HPV6/11/16/18/31/33/45/52/58)	32.3% (20.4-42.5%)
Persistent infections (12 months)	**Adjusted* VE (95% CI)**
Vaccine types (HPV16/18)	95.3% (84.8-98.5%)
Cross-protective types (HPV31/45)	81.5% (55.3-92.3%)
Cross-protective types (HPV31/33/45)	60.4% (27.1-78.5%)
Vaccine and cross-protectives types (HPV16/18/31/45)	89.4% (78.8-94.7%)
hrHPV types	19.1% (00.6-34.3%)
Types 9-valent vaccine (HPV6/11/16/18/31/33/45/52/58)	47.2% (29.9-60.2%)

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

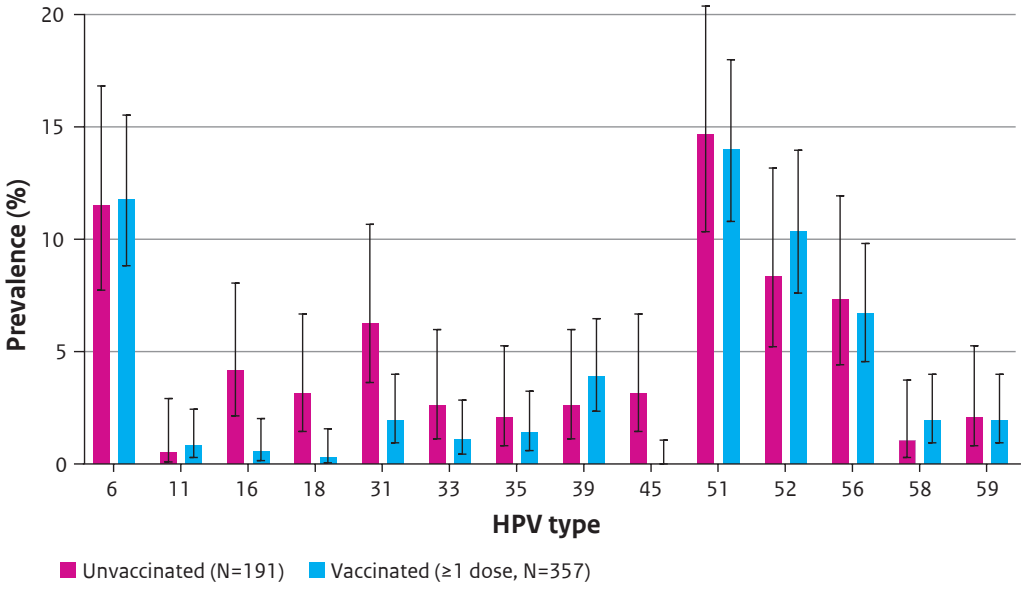

Figure 7.4.4 Anal HPV prevalence by self-reported vaccination status.
[Adapted from: Woestenberg 2019]

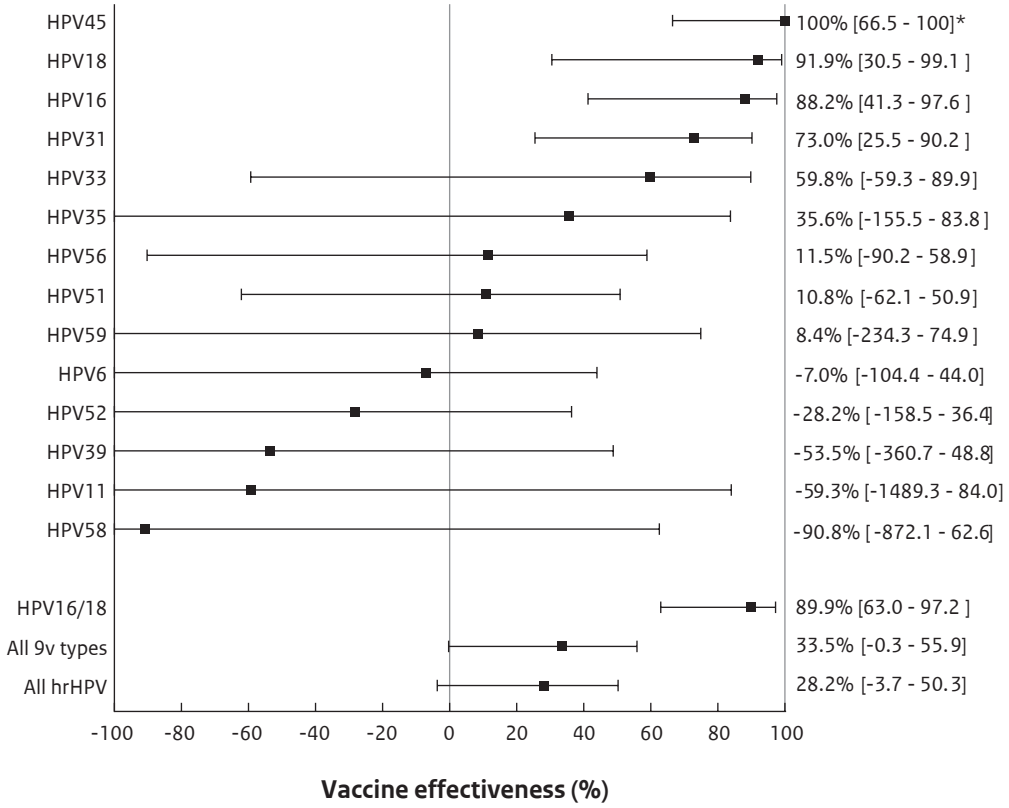

Figure 7.4.5 Adjusted VE against anal HPV for ≥1 dose, with 95% confidence intervals (CIs)

All 9v types includes all HPV types of the nonavalent vaccine: HPV-6/11/16/18/31/33/45/52/58. All high-risk HPV (hrHPV) types includes HPV-16/18/31/33/35/39/45/51/52/56/58/59. *Unadjusted 95% CI based on score confidence limits for the odds ratio.

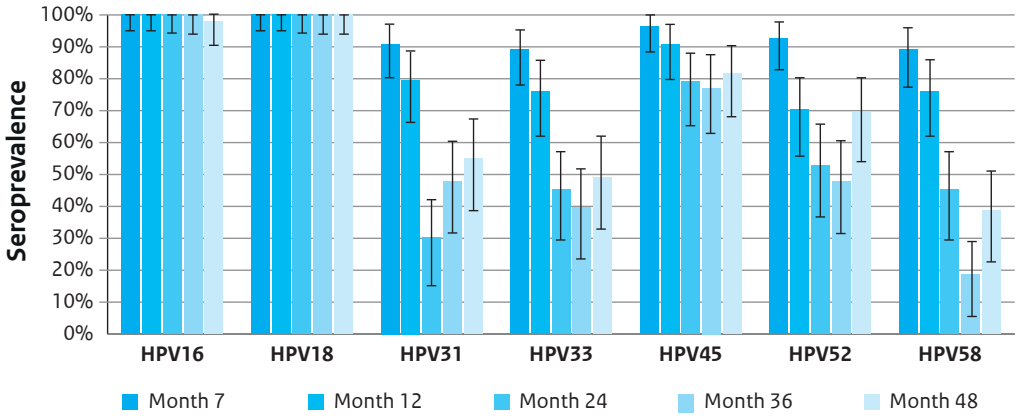

Figure 7.4.6 Seroprevalence among HPV2D participants of HPV types 16/18/31/33/45/52/58 following a two-dose schedule (0, 6 months) at 7, 12, 24, 36 and 48 months after the first dose

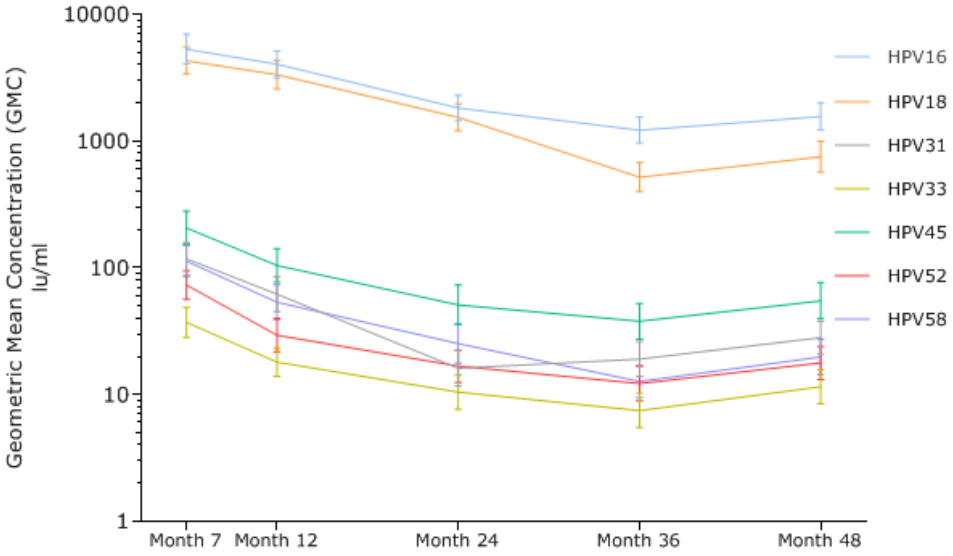

Figure 7.4.7 Geometric Mean Concentrations (GMC; IU/ml) among HPV2D participants of HPV types 16/18/31/33/45/52/58 following a two-dose schedule (0, 6 months) at 7, 12, 24, 36 and 48 months after the first dose

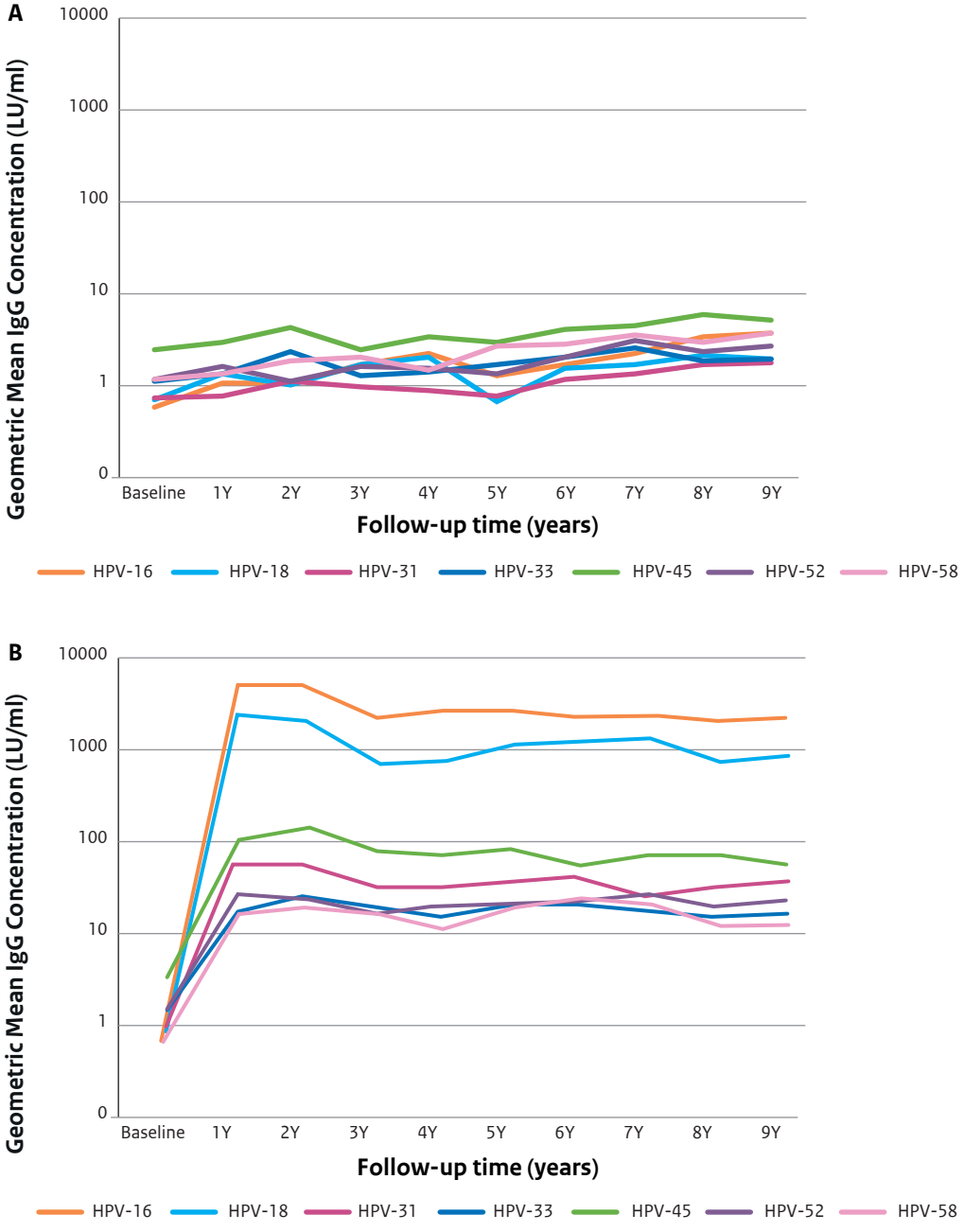

Figure 7.4.8 Geometric Mean Concentrations (GMC; lu/ml) of HPV types 16/18/31/33/45/52/58 after nine years of follow-up among unvaccinated HAVANA participants (A) and three times vaccinated participants (B)

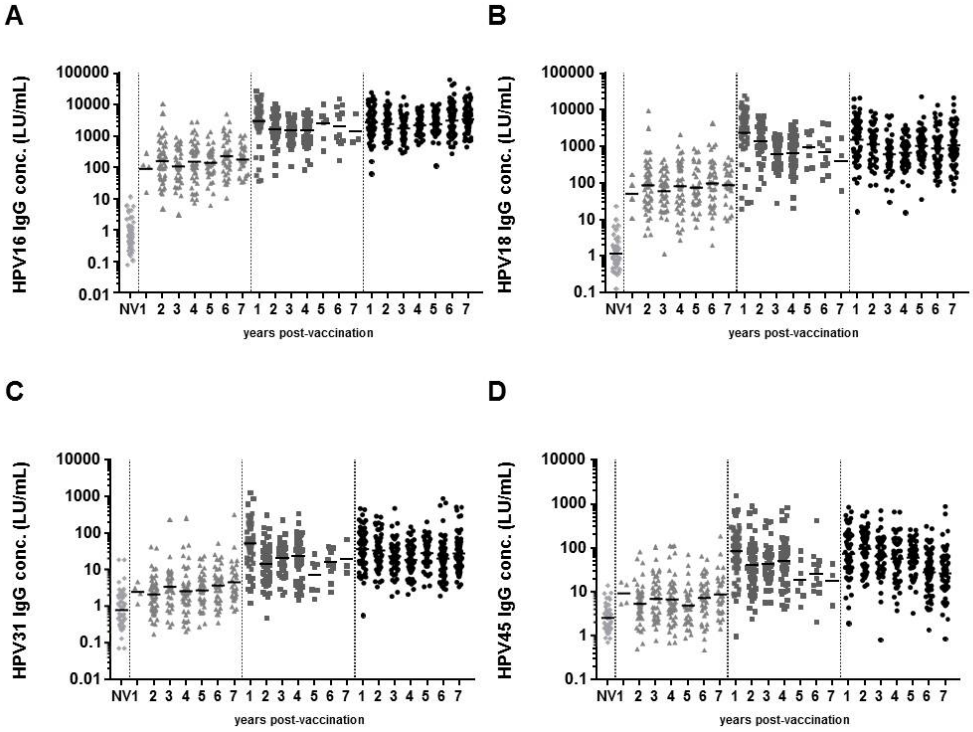

Figure 7.4.9 HPV type-specific IgG concentrations with corresponding GMCs after one, two or three doses of the bivalent HPV vaccine up to seven years post vaccination

HPV16 (A), HPV18 (B), HPV31 (C), and HPV45 (D) specific IgG antibody concentrations (LU/ml) of non- (light grey diamonds), one- (grey triangles), two- (dark grey squares) and three-dose (black circles) 2vHPV vaccinated girls from one to seven years post vaccination. The lines indicate the geometric mean concentrations.

7.4.3 Epidemiology

A persistent infection with a high-risk HPV (hrHPV) type is a necessary cause in the development of cervical cancer. With 569,847 new cases worldwide in 2018, this is the fourth most frequent cancer among women [1]. HPV can also cause cancer to develop at other sites, including vaginal, vulvar, penile, anal, mouth/oral and oropharyngeal cancer. Globally, the relative contribution of hrHPV16/18 is 460,000 corresponding to 72% of all HPV-attributable cases (men and women) [2].

From 2016 onwards, the incidence of cervical cancer in the Netherlands is increasing to 9.14 per 100,000 in 2018 (preliminary data) (Figure 7.4.1). The number of deaths due to cervical cancer increased only slightly in 2018 to 2.51 per 100,000 (preliminary data), compared with 2.39 per 100,000 in 2017 (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 Figure 7.4.2). Annually, approximately 600-850 women in the Netherlands are diagnosed with

cervical cancer and around 200 die due to the disease. The age-specific number of cervical cancer cases and deaths caused by cervical cancer in 2018 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 2018, the number of GW diagnoses at sexual health centres (SHC) was 1,314 [3]. The positivity rate of GW among women (0.71% in 2018) and among men who have sex with men (MSM) (0.67% in 2018) has been declining since 2009, while the positivity rate among heterosexual men (1.98% in 2018) has remained relatively stable since 2013. The number of diagnoses of GW by general practitioners (GPs) was estimated at 42,000 in 2017, while this was 37,500 in 2016.

7.4.4 Recommendations of the Health Council regarding HPV vaccination

In June 2019, the Health Council of the Netherlands issued an update on their previous recommendation regarding HPV vaccination. The aim of the recommendation was to review the HPV vaccination programme in light of current scientific insights and to take into account the HPV-related disease burden in boys and men. Considering both utility and risks in the context of HPV vaccinations, the Health Council recommended extending the current NIP from a girls-only HPV vaccine to gender-neutral HPV vaccination. This would ensure protection for both boys and girls against HPV-related disease. According to the recommendation, vaccination should be offered close to the age of nine years as long-term protection has been shown. In addition, the Health Council recommended offering supplemental HPV vaccination to unvaccinated adults up to 26 years of age. In view of the severity and magnitude of HPV-related cancers, the Health council considers both gender-neutral vaccination and supplemental vaccination a public concern [4]. The Ministry of Health, Welfare and Sports has taken of this advice of the Health Council. Males will be vaccinated in addition to girls and the age of vaccination will be lowered to about 9 years of age. They are also looking into the options for offering unvaccinated boys and girls the vaccination up to 26 years of age.

7.4.5 Current/ongoing research

7.4.5.1 Whole genome sequencing analysis of HPV16 and HPV18

Recent whole genome sequence studies on HPV16- and HPV18-positive genital swabs taken from unvaccinated women revealed a remarkably large population of unique whole genome HPV16/18 variants occurring naturally in young women in the Netherlands [5, 6]. In almost all women a unique variant of HPV16/18 is found. In contrast, within one woman with a persistent infection, strong conservation of the HPV16 or 18 consensus variant sequence is found, showing that the consensus viral genome remains stable over three years. At this moment very limited information is available regarding the origins of this large diversity and how these differences in sequence could affect infection outcome. The contrast of extremely high genetic diversity between host and little diversity seen within host is not yet understood, but could suggest limitations of the sequencing techniques. Currently the whole genome sequencing techniques are more advanced, making it possible to perform ultra-deep sequencing that can detect minority variants in one sample. Minority variants are variations of the consensus whole genome sequence that are found to occur in the sample at lower frequencies. Most recent ultra-deep sequencing analyses on previously sequenced HPV16 positive genital swabs

revealed the presence of a multitude of minor nucleotide variations. Currently, the origin of the minority variants and their role in HPV diversity is not well understood. At present, sequencing of HPV16/18 virus found in vaccinated individuals is challenging, most likely due to very low viral loads. It is not known if differences occur in HPV16/18 variants found in vaccinated individuals. As sequencing techniques evolve, we hope to resolve HPV16/18 variants in the vaccinated population in the near future.

7.4.5.2 HPV amongst vaccinated and unvaccinated adolescents (HAVANA)

A prospective cohort study (HAVANA) among vaccinated and unvaccinated 14- to 16-year-old girls eligible for the catch-up campaign, which started in 2009, 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 three-times vaccinated and unvaccinated young women. Vaginal self-swabs collected in this cohort were tested for the presence of HPV DNA. Vaccine effectiveness (VE) against incident and persistent infections is determined every year. The bivalent vaccine shows a significantly high VE against both incident and 12-month persisting vaccine type infections (HPV16/18) up to eight years post vaccination. High VE against cross-protective types is observed (HPV31/45) as well. All (pooled) VE estimates up to eight years post vaccination against both incident and persistent infections are shown in Table 7.4.1. About half of the participants in this cohort also provide serology samples, which are tested for antibody levels against HPV16/18/31/33/45/52/58. Figure 7.4.8 shows high and stable antibody levels up to nine years post vaccination for HPV16/18 (preliminary results). In addition, higher antibody concentrations against HPV types not included in the bivalent vaccine are observed among vaccinated compared to unvaccinated participants.

In 2016, a second prospective cohort study (HAVANA2) was started among vaccinated and unvaccinated girls (birth cohort 2001). These girls were the first eligible for the two-dose HPV vaccination schedule, which was initiated in 2014. Annual follow-up of this cohort is planned for a period of at least five years, in which the girls are asked to complete a questionnaire and hand in a vaginal self-swab annually. In all, 39,261 girls were invited to participate in the first round of this study. In the first three years of follow-up (FU), 1,577 girls provided a self-sample every year (53.2% vaccinated). The cumulative incidence after three years for hrHPV (HPV16/18 /31/33/35/39/45/51/52/56/58/59) was 6.1% among unvaccinated and 4.5% among vaccinated. The cumulative persistence of hrHPV was 1.5% for unvaccinated and 0.5% for vaccinated. In the third year of the study, prevalence was highest for hrHPV type HPV51, both among vaccinated (1.8%, 95% confidence interval (95% CI) 1.0-2.7%) and unvaccinated (2.6%, 95% CI 1.6-3.7%) participants. A total of 10 HPV16 infections (8 among unvaccinated, 2 among vaccinated participants) and 6 HPV18 infections (all among unvaccinated) was detected during 3 year FU.

7.4.5.3 Performance of HPV detection of HPV type 59 with the SPF10 system

The broad spectrum L1-based SPF10-DEIA LIPA system is widely used for HPV detection and typing in many epidemiological studies, including the studies performed by the RIVM. This assay is known to be highly sensitive for most high-risk HPVs but is less sensitive at detecting HPV59 infections. We have investigated the sensitivity of this system with regard to the

detection of HPV59 infections and compared it to detection with a type-specific qPCR assay. Missed HPV59 infections had significant lower viral loads. Preliminary data suggests that HPV59 infections in non-vaccinated participants were missed more frequently with the SPF10 detection system. HPV59 infection detection is probably hampered more severely in non-vaccinated participants due to the presence of multiple HPV types in these persons. VE measurements of the bivalent HPV vaccine against HPV59 infections based on both detection methods show a clear impact on the VE in preliminary results. This suggests that the qPCR method is unmasking HPV59 infections. The performance of the SPF10 test for HPV45 detection is currently also under investigation in a similar way.

7.4.5.4 Anal HPV among young visitors of sexual health centres (PASSYON study)

Using data from the PASSYON study, a biennial cross-sectional survey conducted among 16- to 24-year-old visitors of sexual health centres in the Netherlands [7], we estimated the direct VE against anal HPV positivity. We used data from women who were eligible for HPV vaccination (cohorts born from 1993 onwards) with a self-reported vaccination status and who provided an anal swab sample (n=548). We used the same methods to estimate the VE against anal HPV positivity as previously used to estimate VE against cervicovaginal HPV positivity [8]. In summary, we calculated odds ratios (ORs) using logistic mixed models with a random intercept, incorporating all clinically relevant HPV types (high-risk HPV types and HPV6/11). VE was calculated as 1 minus the adjusted OR times 100%. Of the women included, 65% reported to have been HPV-vaccinated at least once. Anal HPV prevalence and the adjusted VE against anal HPV positivity are presented in Figure 7.4.4 and Figure 7.4.5. The VE against anal HPV16/18 was high (89.9%) and comparable to the VE against cervicovaginal HPV16/18. In addition, significant cross-protection against anal HPV45 (100%) and HPV31 (73%) was found [9]. These findings are promising for anal cancer control, given that nearly 90% of all HPV-related anal cancers are associated with HPV16/18 [2].

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

To monitor the quality and quantity of the generated immune response following a two-dose vaccination schedule, a cohort study among the first birth cohort that was eligible for vaccination with a two-dose schedule, i.e. birth cohort 2001, started in 2014. Girls donate a blood sample and complete a questionnaire every year. To date, results are available up to the fourth year. These results show high seroprevalence and antibody levels against vaccine types HPV16/18 up to 48 months of follow-up (Figure 7.4.6 and Figure 7.4.7). However, waning antibody levels were observed until 36 months. In month 48, levels remained stable (Figure 7.4.6). Seroprevalence and antibody levels were considerably lower for HPV types 31, 33, 45, 52, 58, with a somewhat higher level of waning (Figure 7.4.6 and Figure 7.4.7).

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

The HPV1D-study, a cross-sectional study monitoring the immunogenicity of one-dose bivalent HPV-vaccinated girls in the Netherlands, was conducted in 2017. This study shows that a one-dose schedule is immunogenic up to seven years post vaccination. However, it results in considerably lower antibody responses and lower B- and T-cell memory when compared to the two- and three-dose vaccinated girls (Figure 7.4.9). Therefore, one-dose vaccinated girls

might be at higher risk for waning immunity to HPV on the long-term during life.

7.4.5.7 *Modelling*

HPV vaccines have demonstrated high efficacy in protecting against infection and diseases related to the vaccine types. However, HPV vaccination may trigger type replacement by non-vaccine types if different types interact competitively [10]. So far, based on the lack of systematic increases in non-vaccine-type prevalence in the first decade following HPV vaccination [11] and the presence of cross-protection for some non-vaccine types [12], the risk of type replacement has been deemed low. However, it is unclear to what extent these observations rule out type replacement in the long run.

To investigate the relationship between type replacement and early post-vaccine surveillance, we constructed a transmission model in which a vaccine and a non-vaccine type compete through natural cross-immunity and simulated HPV vaccination for different levels of cross-immunity, vaccination coverage and vaccine-induced cross-protection to the non-vaccine type. We derived the short-term impacts of vaccination in a form that mimics real-life surveillance and evaluated whether these correctly indicate the occurrence of type replacement in the post-vaccine equilibrium [13].

In our model, the occurrence and timing of type replacement result from a balance between the levels of infection-induced cross-immunity and vaccine-induced cross-protection. Without cross-protection in the model, the presence of cross-immunity leads to type replacement. Type replacement could be prevented through cross-protection if strong enough. However, assuming weak cross-protection may lead to short-term decreases in non-vaccine-type prevalence before rebounding into type replacement. Such a phenomenon of delayed type replacement is analogous to the so-called 'honeymoon period' of vaccination. In addition, a reduced risk of non-vaccine-type infection in vaccinated relative to unvaccinated individuals does not preclude increased prevalence in the population at large. Therefore, although evidence thus far is reassuring, our model indicates that post-vaccine surveillance may still be too short to detect type replacement. Monitoring of non-vaccine-type transmission remains pivotal.

7.4.5.8 *Male vaccination*

Indications for HPV vaccination programmes are expanding to boys in an increasing number of countries or jurisdictions. However, the rationale behind their inclusion is often unclear. Using a Bayesian synthesis framework and assuming equal vaccine coverage in both sexes, we assessed how the incremental number of cancer cases prevented and life-years gained from boys' vaccination are distributed between women, heterosexual men, and MSM in the Netherlands. Below 60% coverage, at least 50% of the gains from boys' vaccination were attributable to cervical cancer prevention, whereas at 80% coverage, 50% of the gains were attributable to women, 15% to heterosexual men, and 35% to MSM. Above 90% coverage, 85–100% of the gains from boys' vaccination were attributable to anal and oropharyngeal cancer prevention, mainly in MSM. Sex-neutral vaccination can thus be advocated on grounds of bolstering herd protection for women and directly protecting men, particularly MSM, with

the clinical significance of either argument determined by the coverage [14].

Model input parameters regarding HPV attributable fractions to HPV associated cancers are often derived from original molecular-epidemiological studies [15-19]. For the analyses described above, the following cancer site specific HPV attributable fractions (any HPV type) with their respective source were considered for model input: cervical cancer 96%, anus cancer 87.5% [15], oropharyngeal cancer 29.1% [16], vulva cancer 18.3% [17], vagina cancer 71.0% [18], and penis cancer 25.1% [19]. However, attributable fractions reported in the original molecular-epidemiological studies fluctuate, for example due to differences in the applied definition, molecular assay, or actual variation between populations.

The opportunity of selectively vaccinating MSM against oncogenic HPV strongly depends on timely implementation and on the effectiveness of prophylactic vaccines when given after sexual debut. Only a few studies have investigated the potential impact of targeted vaccination for preventing anal cancer in MSM populations, with equivocal results [20-22]. The recommendation, which is based on a modelling study [22], that vaccinating HIV-positive MSM up to age 40 would likely be cost-effective in the UK is challenged by recently published empirical data on the lack of efficacy in HIV-positive MSM aged 27 years or older [23]. Accordingly, a recent systematic review presents the HPV vaccine as 'a potentially cost-effective strategy for preventing mainly –but not limited to– anal cancer in MSM populations' but also stresses 'a need for additional robust data and further studies for more countries' [24].

We present such an assessment by employing a multi-modelling approach that is informed by a cohort study on HPV infection among MSM in Amsterdam, and by scenarios of vaccine uptake derived from a targeted hepatitis B vaccination campaign in the Netherlands [25]. Our projections suggest that targeted vaccination may reduce the prevalence of anogenital HPV16 infections, which are responsible for the majority of HPV-related cancers in MSM, by 30% to 50% depending on the level of recruitment of MSM into a targeted vaccination campaign. Moreover, targeted vaccination achieved considerably faster reductions compared to sex-neutral vaccination in preadolescence, if started simultaneously. The reduction in anal HPV16 prevalence amounted to 75% under a combined vaccination strategy. HPV16 prevalence reductions mostly exceeded vaccine coverage projections among MSM, illustrating the efficiency of prophylactic immunisation even when the HPV vaccine is given after sexual debut.

7.4.6 International developments

7.4.6.1 Impact of HPV vaccination

A recent study from Mesher and colleagues (United Kingdom) showed significant reductions in prevalent HPV16/18 infections and high VE eight years after the introduction of a national bivalent vaccination programme (2008). Using residual vulva-vaginal swabs from women (aged 16-24 year) who attended for chlamydia screening between 2010 and 2016, a decline in HPV16/18 between 2010/2011 and 2016 was shown depending on age (8.2% to 1.6% in 16-18 year olds and 14.0% to 1.6% in 19-21 year olds, respectively). Declines were also seen for HPV31/33/45 (6.5% to 0.6% for 16-18 year olds and 8.6% to 2.6% for 19-21 year olds). Vaccine effectiveness for HPV16/18 infection was 82.0% (95% C.I. 60.6-91.8%) and 48.7% for

HPV31/33/45(95% C.I. 20.8-66.8%) [26]. This study provides another confirmation of the effectiveness of bivalent vaccination against HPV16/18 infections in the general population as well as a cross-protective effect on non-vaccine types. Moreover, in Japan, VE against HPV infection six years post bivalent vaccination introduction was shown for the first time based on verified vaccination data [27]. HPV tests were performed on women attending for cervical screening (20-22 years old). In women sexually naive at vaccination (3 times vaccinated), pooled and adjusted VEs were 93.9% and 67.7% for HPV16/18 and HPV31/45/52, respectively. This is an important finding as vaccine coverage in Japan has been low (dropping from >70% after introduction of the vaccine to <1% in April 2013), after the Japanese government suspended its proactive recommendation. High VE estimates derived from the Japanese population could aid in improving uptake.

Furthermore, data from the United Kingdom implies an effect of the national female-only vaccination programme in the prevention of oropharyngeal HPV16 infections. Study participants were recruited in six hospitals for undergoing tonsillectomy for non-malignant indications. Oral samples were collected and tested for HPV and combined with vaccination data. Among the 312 participants (12–24 year-olds) were 189 vaccinated females (of whom 89% received the bivalent vaccine) and no vaccinated males (n=69). Oropharyngeal HPV-16 prevalence was significantly lower in vaccinated versus unvaccinated females (0.5% vs 5.6%, P = .04), while prevalence of any oropharyngeal HPV type was comparable between these groups. Oropharyngeal HPV-16 prevalence in unvaccinated males was similar to vaccinated females, and lower than unvaccinated females (0% vs 5.6%, P = .08). Besides the effect of HPV vaccination on HPV16 oral infections in vaccinated females, this study also suggests potential herd immunity in contemporaneously aged males [28].

A Scottish retrospective population study used data from the National vaccination and cervical screening programmes to quantify the effect of the bivalent vaccine on cervical disease at age 20 years. Vaccinated women in the routine vaccination programme (1995-1996) and vaccinated women from the catch-up campaign (1990-1994) were compared with unvaccinated women (1988-1989) based on smear test result. The VE was estimated for cytology results and associated histological diagnoses. When comparing unvaccinated women with routinely vaccinated women, an 89% reduction (95% C.I. 81-94%) in prevalent cervical intraepithelial neoplasia (CIN) 3 or worse was observed. Also, significant reductions were observed for CIN2 (88% reduction (95% C.I. 83-92%)) and CIN1 (79% reduction (95% C.I. 69-86%)). The vaccine effectiveness was higher among women vaccinated at age 12-13 (routine programme) compared to those vaccinated at age 17 (catch-up campaign). This study is important in showing the clinical impact of the bivalent vaccine on pre-invasive cervical disease in girls routinely vaccinated. Also herd immunity among non-vaccinated women form birth cohorts 1995-1996 was observed [29].

A recently published review and post-hoc analysis from phase III trials of HPV vaccines conducted by GSK considered the efficacy of the bivalent and quadrivalent vaccine on non-vaccine type caused CIN. CIN lesion counts from phase III trials were extracted and divided into three categories: (1) containing at least one vaccine HPV type, (2) containing at least one

vaccine HPV type and a high-risk non-vaccine type (co-infections), and (3) containing no vaccine types (non-vaccine or no high-risk HPV types). Cross-protective efficacy against CIN3 among HPV naive subjects was calculated and ranged from 81.3% (95%CI: 34.7-96.5%) (excluding co-infections) to 88.5% (95%CI:62.4-97.8%) (including co-infections) for the bivalent vaccine. For the quadrivalent vaccine, efficacy ranged from -58.7% (95%CI: -180.5-8.5%) (excluding co-infections) to 13.1% (95%CI: -39.0-45.9%) (including co-infections). When considering all endpoint levels irrespective of HPV type, the bivalent vaccine showed higher efficacy overall, although the difference was most pronounced for CIN3 in the naïve cohorts; 92.1% (95% CI: 75.2-98.4%) for the bivalent vaccine compared with 43.0% (95% CI: 12.9-63.2%) for the quadrivalent vaccine. The authors (who all have GSK as affiliation) suggest the higher efficacy can be explained by the different adjuvantia that are used in the vaccines [30].

A recent systematic review and meta-analysis covering over 60 million people focused on the impact of national HPV vaccination programmes [11]. It clearly showed the effectiveness at the population level of the bivalent and quadrivalent vaccines up to eight years after implementation; HPV16/18 infections had reduced by 83% and HPV31/33/45 infections by 54% among 13- to 19-year-old girls. Moreover, a strong decline in CIN2+ prevalence was observed among screened girls and women, as well as a declining trend of anogenital wart diagnoses among men and women.

7.4.6.2 One-dose schedule

A two-dose vaccination schedule is currently used most often in national immunisation programmes worldwide. Starting a few years ago, however, increasing attention has been devoted to a one-dose HPV vaccination schedule. In several studies, one-dose recipients showed robust and sustained antibody levels against HPV16 and HPV18 over a nine-year period. Although inferior to that in two- and three-dose vaccinated girls, the incidence of HPV16 and HPV18 infections were similar and uniformly low in all the dose groups up to seven years [31-33]. Moreover, HPV-specific cellular immunity was still present up to six years following a one-dose schedule [34].

The data suggest that a single dose of the bivalent or quadrivalent HPV vaccine is immunogenic and could provide long-lasting protection against HPV-vaccine type infections. However, it is important to keep in mind that the numbers of individuals that received only one dose are still relatively small. The next step in one-dose HPV vaccination research should therefore focus on randomised controlled trials to evaluate the protection afforded by a single dose of HPV vaccine.

7.4.6.3 Cost-effectiveness

De la Fuente et al evaluated the epidemiological impact and cost-effectiveness of a girls-only and a gender-neutral vaccination programme with 9vHPV in Spain [35]. The 9vHPV vaccination strategy was compared with the current 4vHPV vaccination programme in Spain, using a payer perspective, a 100-year time horizon, and 78% vaccination coverage. A girls-only vaccination strategy at age 12 with 9vHPV was found to be a cost-effective strategy compared with 4vHPV: the incremental cost-effectiveness ratio (ICER) was €7,718 per quality-adjusted life year (QALY).

The ICER of a gender-neutral vaccination scenario with 9vHPV compared with girls-only vaccination scenario with 9vHPV was €53,244/QALY. In the sensitivity analysis, vaccination uptake, discount rate, and inclusion of head and neck cancers had the greatest impact on the ICER. This study was funded by Sanofi Pasteur MSD Spain and MSD Spain.

In the United States, routine HPV vaccination is recommended for females and males at age 11 or 12 using 9vHPV. Vaccination is also recommended for females up to 26 years of age, and males up to 21 years of age. Chesson et al assessed the health impact and cost-effectiveness of harmonising female and male vaccination recommendations by increasing the upper recommended catch-up age for HPV vaccination in males from 21 to 26 years of age [36]. Compared to no vaccination, providing 9vHPV for females 12-26 years of age and males 12-21 years of age led to an ICER of $16,600 per QALY gained. The estimated cost per QALY gained by expanding male vaccination through 26 years was not cost-effective: $228,800 ranging from $137,900 to $367,300 in multi-way sensitivity analyses.
In another study, Chesson et al reviewed and summarised recent cancer cost estimates [37]. They found that applying the higher current cancer cost estimates had a notable impact on the estimated medical costs averted by HPV vaccination and a moderate impact on the estimated cost per QALY gained by HPV vaccination. For example, for catch-up vaccination of teenagers and young adults, applying the more recent cancer costs reduced the estimated cost per QALY gained by about $12,400.

There is increasing interest in estimating the broader benefits of public health interventions beyond those captured in traditional cost-effectiveness analyses. In principle, cost-benefit analysis (CBA) offers a way to capture such benefits but a wide variety of methods have been used to monetise benefits in CBAs. Park et al conducted a CBA for HPV vaccination in the United Kingdom using eight methods for monetising health and economic benefits [38]. If Dutch guidelines were applied, that is using the human capital method and monetising quality-adjusted life years, vaccination would be cost-saving.

7.4.6.4 Screening uptake

A Dutch non-inferiority trial evaluated clinical accuracy of primary HPV testing on self-collected samples in a screening setting [39]. Women aged 29-61 from the regular screening were invited and randomly allocated to either a self-sampling group or a clinician-based sampling group. The relative risk for testing HPV positive was 1.04 (95% CI 0.92–1.17). For both CIN2+ and CIN3+, the sensitivity and specificity of HPV testing did not differ between self-sampling and clinician-based sampling (CIN2+: relative sensitivity 0.96 [0.90–1.03]; relative specificity 1.00 [0.99–1.01]; CIN3+: relative sensitivity 0.99 [0.91–1.08]; relative specificity 1.00 [0.99–1.01]). This study shows that self-collected samples and clinician-collected samples result in similar accuracy with regard to detection of CIN2+ or CIN3+.

7.4.7 Literature

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* RIVM publication

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7.5 Measles

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7.5.1 Key points

- The number of measles cases is rising, with 24 reported cases in 2018 and 45 in the first six months of 2019.
- A local outbreak in a low-vaccination municipality started in June 2019, with 11 patients reported in that month.
- Ten of the 69 patients in the reporting period were too young to be vaccinated.
- Genotypes B3 and D8 were detected, which are the two genotypes that are also detected most frequently in other European countries.

7.5.2 Tables and figures

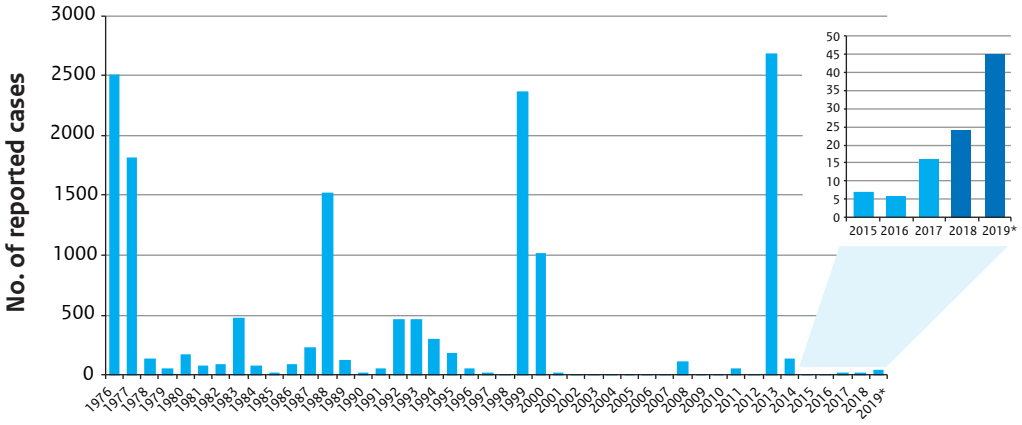

Figure 7.5.1 Annual reported measles cases since the introduction of measles in the Dutch vaccination programme

* up to July

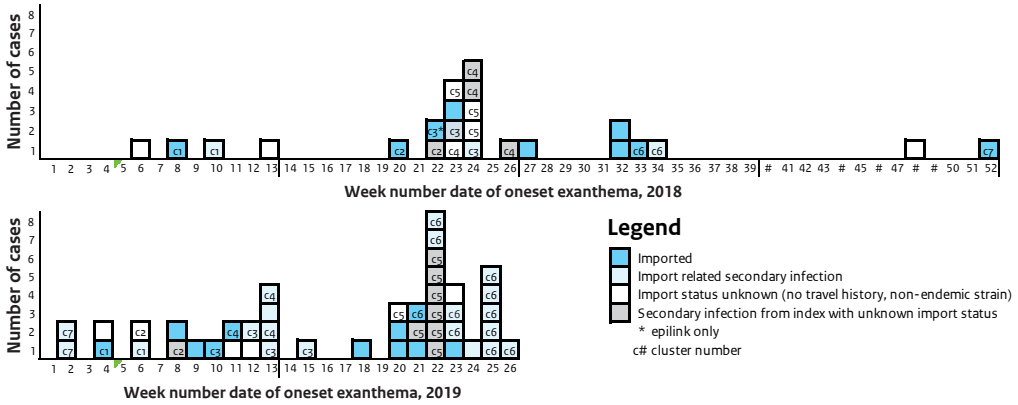

Figure 7.5.2 Epidemic curve of reported measles cases in 2018 and the first six months of 2019 by week of onset and import status

Table 7.5.1 Characteristics of measles patients reported from 2015 up to 1 July 2019

	2015	2016	2017	2018	1st half 2019	Total
Number	7	6	16	24	45	98
Age (median)	32	20	30	26	24	28
Import status						
Imported	5	4	6	9	12	36
Import-related	2	1	3	5	20	31
Unknown	0	1	7	10	13	31
% import(-related)	*100%*	*83%*	*56%*	*58%*	*71%*	*68%*
Epidemiological cluster						
Part of a cluster	0	2	8	17	33	60
Solitary case	7	4	12	7	12	42
% in cluster	*0%*	*33%*	*50%*	*71%*	*73%*	*61%*
Genotype						
B3	1	0	3	12	0	16
D8	4	4	10	9	36	63
Unknown	2	2	3	3	9	19
% genotyped	*71%*	*67%*	*81%*	*88%*	*80%*	*81%*

	2015	2016	2017	2018	1st half 2019	Total
Vaccination status						
Too young for vaccination	0	0	0	5	5	10
Not vaccinated	5	3	12	10	18	48
1 dose	1	2	1	4	9	17
2 or more doses	0	0	2	3	7	12
# doses unknown	0	0	0	0	1	1
Unknown	1	1	1	2	5	10
% vaccinated	*14%*	*33%*	*19%*	*29%*	*38%*	*31%*

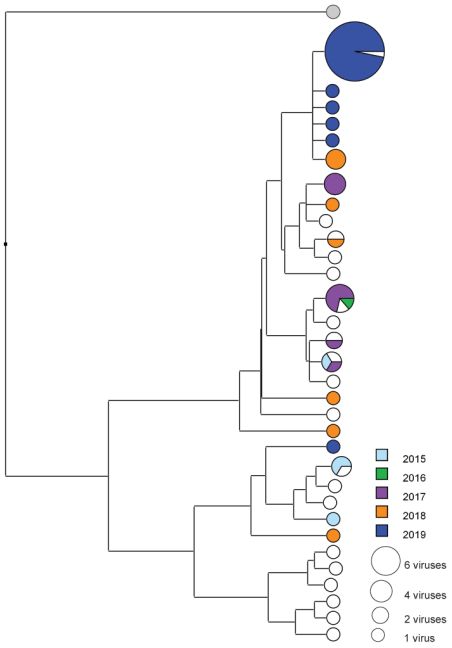

Figure 7.5.3 Dendogram by UPGMA (unweighted pair group method with arithmetic mean) based on the nucleotide sequences of a part of the N gene (450 nucleotides) of 60 genotype D8 measles viruses detected in the Netherlands in 2015-2019 (marked with colours), and epidemiologically relevant genotype D8 sequence variants of measles viruses from the past years ('named strains', globally; marked in white). The size of the circles indicates the number of viruses and the colour of (parts of) the circles stands for the year of detection. The virus marked grey is a genotype D1 measles virus; MVi/Bristol.GBR/0.74, used as outgroup. The dendogram was created in BioNumerics version 7.6.3.

7.5.3 Epidemiology

The number of measles cases has increased in the past two years, from 24 cases reported in 2018 to 45 cases in the first six months of 2019 (Figure 7.5.1). Table 7.5.1 summarises the characteristics of measles cases reported in the past five years. In both 2018 and the first half of 2019, the mean age of the patients was 22 years (range 0-51 years).

An epidemic curve of the cases in 2018 and the first half of 2019 is shown in Figure 7.5.2. In 2018, nine cases were imported with measles acquired in Italy (n=2), Romania (n=2), and one each from Greece, India, Poland, Portugal, and Ukraine. Four of these patients led to secondary infection of five individuals in total. Ten patients were infected by an unknown source in the Netherlands. One of these led to a cluster with two secondary infections and one tertiary infection. In the first six months of 2019, 12 patients acquired the infection abroad, namely in Poland (n=3), Belgium (n=2), France (n=2), Ukraine (n=2), Israel, South Africa, and Turkey. Four of these imported infections led to onward transmission, infecting 17 others. Overall, 58% of the measles cases in 2018 and 71% of those in the first half of 2019 were imported or import-related. In 2019, seven clusters were identified including a total of 33 patients. One cluster in May 2019 occurred in a work setting and included 8 patients born between 1974 and 1980. Another large cluster started in June 2019 in a municipality with low vaccination coverage. Up to the end of June 2019, eleven patients were reported, mainly unvaccinated children born after 2012 (i.e. just before or after the last epidemic).

Of the cases reported in 2018, 15 (63%) were unvaccinated. Five of them were 14 months or under and therefore too young to be vaccinated. Seven patients (29%) were reportedly vaccinated, although four of these with only one dose. The vaccination status of two patients was unknown. Thirteen patients were hospitalised, including the five children who were too young to be vaccinated. Two (15%) of the hospitalised patients were vaccinated, one with one dose and one with three doses.

In the first half of 2019, 23 cases (58%) were unvaccinated, five of which were too young to be vaccinated. Seventeen patients were vaccinated, slightly more than half of these with one dose. The seven patients vaccinated with at least two doses were all secondary infections. Three of them were children in the June 2019 cluster who had received measles vaccination under 12 months of age (MMR0) during the last outbreak in 2013-2014, and the routine MMR1 at 14 months of age. Vaccinated patients had mild disease and were generally less ill than unvaccinated patients. Nine patients were hospitalised, three (33%) of these were vaccinated with one or an unknown number of doses.

As of mid-2019, two cases of subacute sclerosing panencephalitis (SSPE) are known to have occurred after measles infection during the last epidemic in 2013-2014. SSPE is a rare form of chronic progressive brain inflammation caused by measles virus, a fatal complication that occurs on average six years after measles infection [1].

7.5.4 Pathogen

The genotype of the detected measles virus of 21 (88%) reported cases in 2018 and 36 (80%) reported cases in the first six months of 2019 was determined. In 2018, measles virus genotype B3 was detected in 12 cases and measles virus genotype D8 was detected in three cases. In 2019, only measles virus genotype D8 was detected. Measles viruses of genotypes B3 and D8 were also the two genotypes that were detected most often in Europe and worldwide in 2018 and 2019 based on sequence data available in the global Measles Nucleotide Surveillance (MeaNS) database [2, 3]. In almost all measles virus cases in the Netherlands in 2018, the obtained nucleotide sequence data from measles viruses supported the epidemiological data about a possible origin of infection or could provide additional information about a possible link to measles virus cases in other countries for which recent measles virus nucleotide sequence data were available in the MeaNS database. However, of the 36 genotype D8 sequences detected in 2019, 29 (81%) were identical (Figure 7.5.3). This exact sequence was detected in a high number of measles cases worldwide recently. Therefore, data from the molecular surveillance for the first half of 2019 based on a relatively small part of the genome are of limited value to determine if measles virus is circulating in the Netherlands or if we are seeing multiple import cases. Currently different methods are being explored to sequence additional parts of the genome with the aim of increasing molecular resolution.

7.5.5 Research

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

Young unvaccinated children who were at increased risk of measles during the latest measles epidemic in the Netherlands were offered an early MMR vaccination (<12 months in addition to the routine dose at 14 months) to provide immediate immune protection. However, these children showed a slightly stronger waning of antibody concentrations over time (between 2 and 4 years of age) than children with a first MMR dose at age 14 months. Children vaccinated below 9 months of age in particular had lower neutralising antibody concentrations at four years of age compared with infants vaccinated at a later age, despite an additional vaccination at 14 months of age [4, 5]. In conclusion, early MMR vaccination (<12 months of age) provides immediate protection in the majority of infants but the susceptibility to measles virus infection among early vaccinated individuals may increase with age, consequently herd immunity in the population might be adversely impacted in the long term.

The cellular basis of acquired measles immunity following early and routine MMR vaccination is currently being investigated in more detail. Furthermore, a follow-up study of children that received early MMR vaccination during the 2013-2014 epidemic was recently approved by METC and will start mid-2019.

7.5.5.2 Immunological amnesia after measles virus infection

A study by Erasmus MC involving 23 unvaccinated children with measles in the last outbreak showed that measles infection had an impact on circulating lymphocyte subsets that can last for at least a month after recovery from the disease. They found reduced frequencies of circulating memory B cells and increased frequencies of regulatory T cells and transitional B cells after measles, assumed to result from the infection of specific lymphocyte subsets during

the acute stage of infection. While these investigations were performed within a time frame of one month post onset of measles, these data support the researchers' previously published hypothesis that measles virus infection causes immunological amnesia by infecting and depleting pre-existing memory lymphocytes, possibly exerting a long-term negative effect on host resistance [6].

7.5.5.3 *Measles among vaccinated people*

A report from Portugal highlighted that in measles outbreaks early in 2018 involving 112 patients, 87% were vaccinated [7]. The outbreaks occurred in healthcare settings and it was noted that almost half of the patients (45%) presented a combination of symptoms that did not match the EU clinical case definition. The case definition for measles is rash and fever, and at least one of the three C's (cough, coryza or conjunctivitis). Around 1 in 5 patients presented with rash and fever or with rash only.

The clinical presentation of measles among vaccinated people has also been studied in the US. Out of 232 measles cases with a verified vaccination status reported in the period 2000-2015, 80% were unvaccinated, 9% had had 1 dose of measles vaccine, and 11% had had ≥2 doses of measles vaccine. Patients who were vaccinated with two or more doses had lower rates of hospitalisation, cough, coryza, conjunctivitis, and fever than subjects who had received 1 dose of measles vaccine or who were unvaccinated. Onward transmission to unvaccinated contacts is relatively rare but was documented for three of the 26 patients vaccinated with at least two doses [8].

7.5.6 International developments

The EU is experiencing a resurgence of measles, with several outbreaks and fatalities since 2017. In the period 2014-2016, around 4,000 cases were reported annually by all EU/EEA countries combined. In 2017, over 18,000 cases were reported. In 2018, there were over 13,000, and up to May 2019, over 8,000 were reported [9]. Most cases were reported in France, Italy, Greece, and Romania, with more than 2,000 cases each in 2018. In 2017 and 2018, 71 deaths were reported, of which 46 in Romania and 14 in Italy [9]. In the Ukraine a large-scale outbreak is still ongoing in 2019, with over 50,000 cases reported in 2018 [10]. The US reported over 1,000 cases from 1 January to 6 June 2019, which is the greatest number of cases reported since 1992 and since measles was declared eliminated in 2000. The majority of people who were diagnosed with measles were unvaccinated.

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 three cases reported in 2018.
- Since May 2018, MenACWY vaccination at 14 months of age is part of the NIP. Between October 2018 and June 2019, all children born in 2001-2005 have been offered MenACWY vaccination (preliminary uptake ~82%).
- From 2019 onwards, MenACWY vaccination is offered to children in the year they turn 14 years as part of the national immunisation programme.
- Since 2015, the number of cases with meningococcal serogroup W (MenW) disease has been rising, with 103 cases (0.60 per 100,000) and 23 deaths reported in 2018.
- In the first six months of 2019, the incidence of MenW decreased to 0.45 per 100,000 (n=39). A decrease or stabilisation of the incidence was seen in all age groups, except 80+ year olds.
- There have been no MenW cases, either vaccinated or unvaccinated, in the cohorts eligible for MenACWY vaccination since its implementation.
- The incidence of meningococcal serogroup B (MenB) disease has been declining steadily since the late nineties and has stabilised at an incidence of 0.5 per 100,000 since 2011.
- In 2018, 74 cases and 5 deaths of MenB disease were reported, showing a slight increase since 2014 (n=61). The incidence of MenB disease was highest in children aged under 5 years, with 31 cases in 2018 (3.6 per 100,000).
- The Health Council of the Netherlands did not recommend adding MenB vaccination to the NIP due to uncertainty with regard to the effectiveness of the vaccine, the risk of fever and unfavourable cost-effectiveness. The Council recommended reconsidering this advice when new data becomes available.
- The number of cases of meningococcal disease caused by serogroup Y or other serogroups is low and stable.

7.6.2 Figures

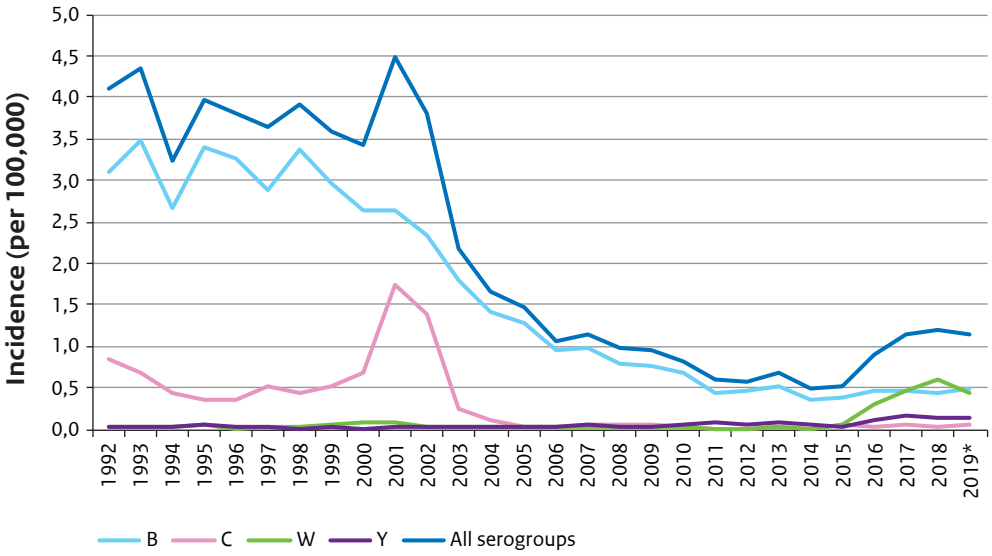

Figure 7.6.1 Incidence of meningococcal disease by serogroup, 1992-2019* (*up to June)

Source: NRLBM

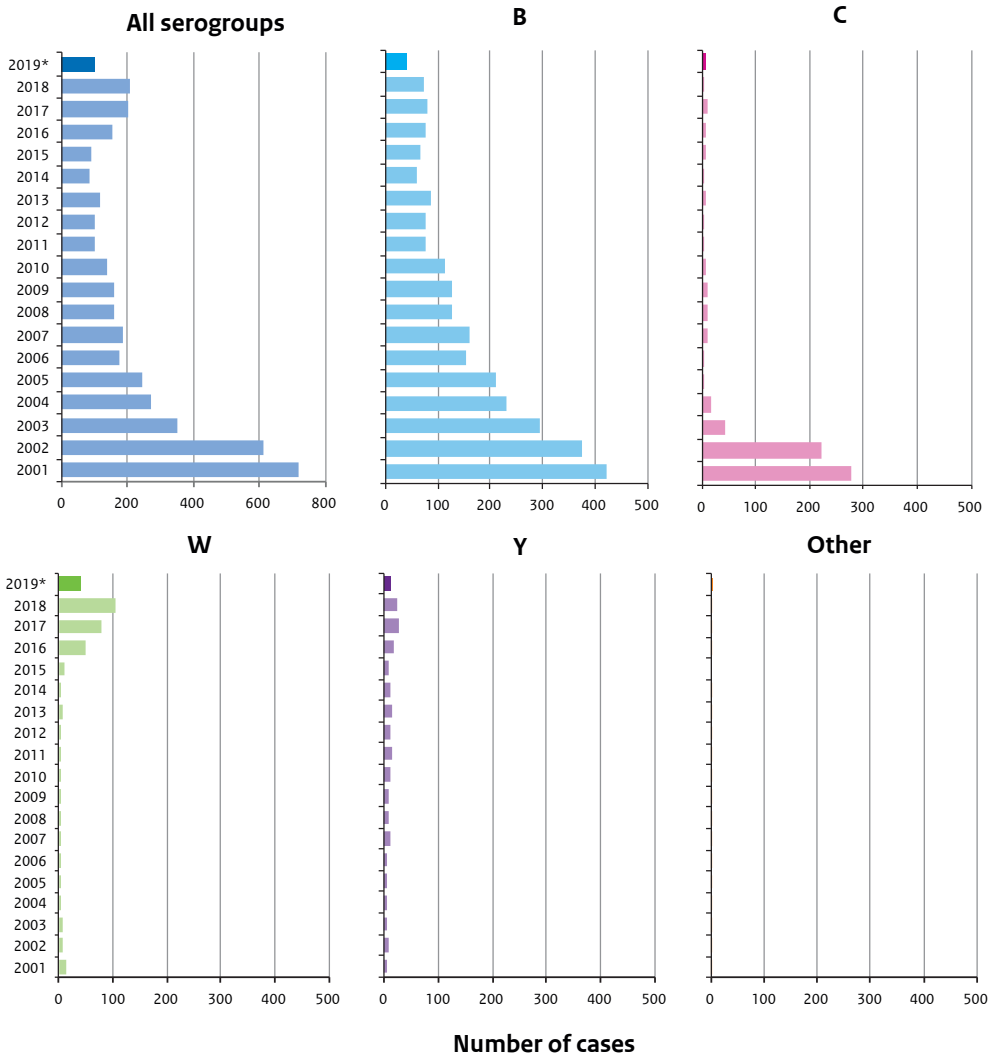

Figure 7.6.2 Number of cases of meningococcal disease by serogroup, 2002-2019* (*up to June)

Note the different scale in the graph with all serogroups

Source: NRLBM

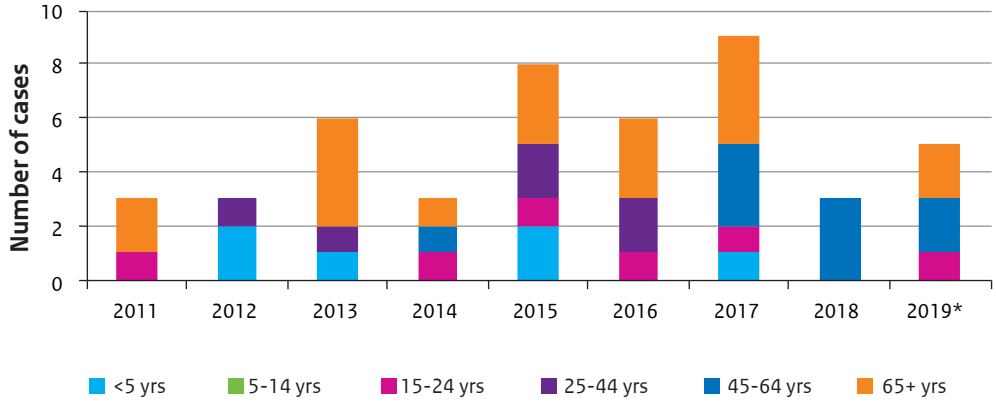

Figure 7.6.3 Number of cases of meningococcal serogroup C disease by age group, 2011-2019* (*up to June)

Source: NRLBM

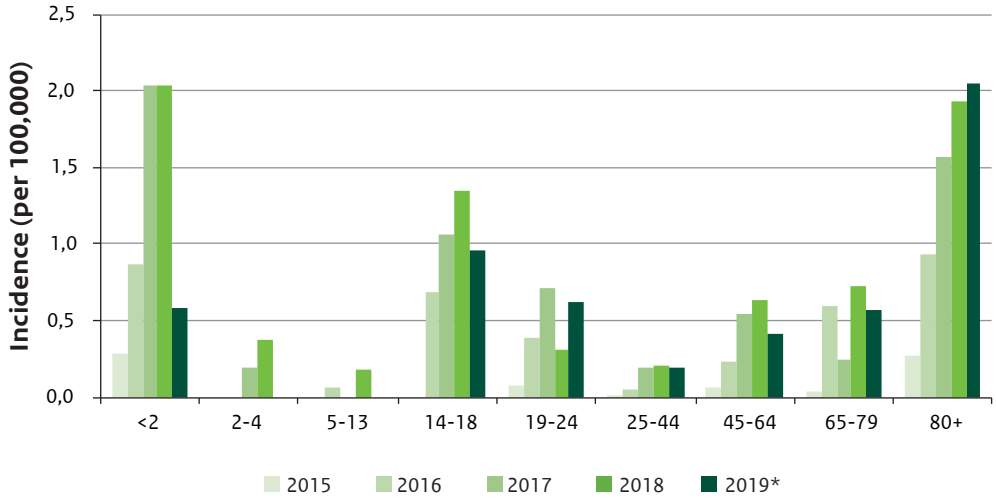

Figure 7.6.4 Age-specific incidence of meningococcal serogroup W disease by year, 2015-2019* (*up to June)

Source: NRLBM

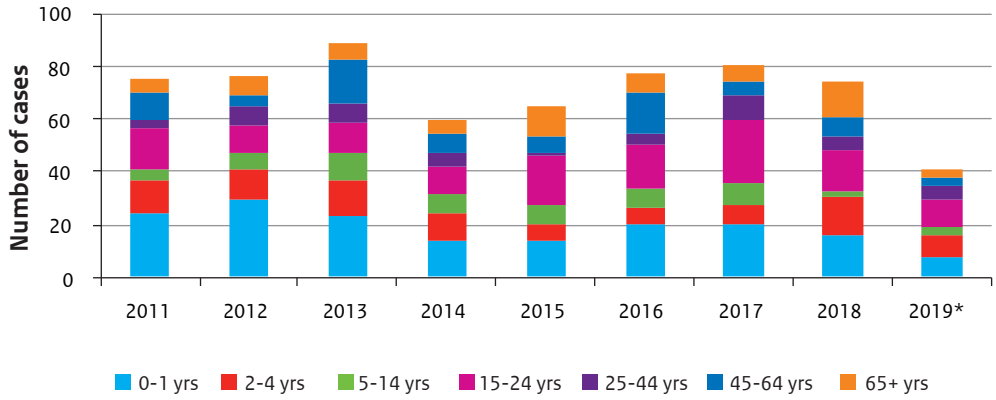

Figure 7.6.5 Number of cases of meningococcal serogroup B disease by age group, 2011-2019* (*up to June)

Source: NRLBM

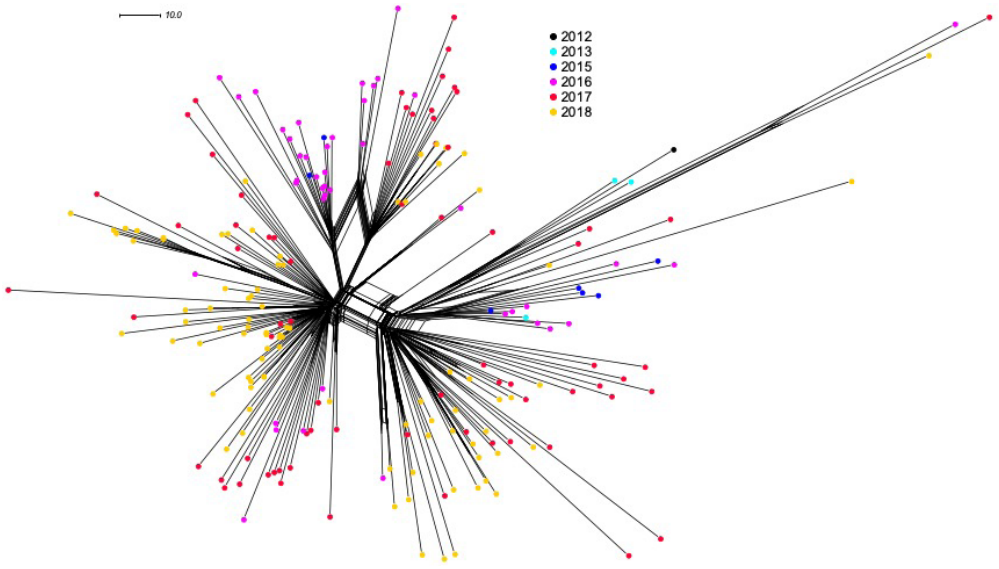

Figure 7.6.6 Neighbour-net phylogenetic network analysis of all available genomes of serogroup W clonal complex 11 isolates from the Netherlands, 2012–2018 (n =213)

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) [1]. The resulting distance matrices were visualised with SplitsTree4 version 4.13.1 [2].

Source: NRLBM

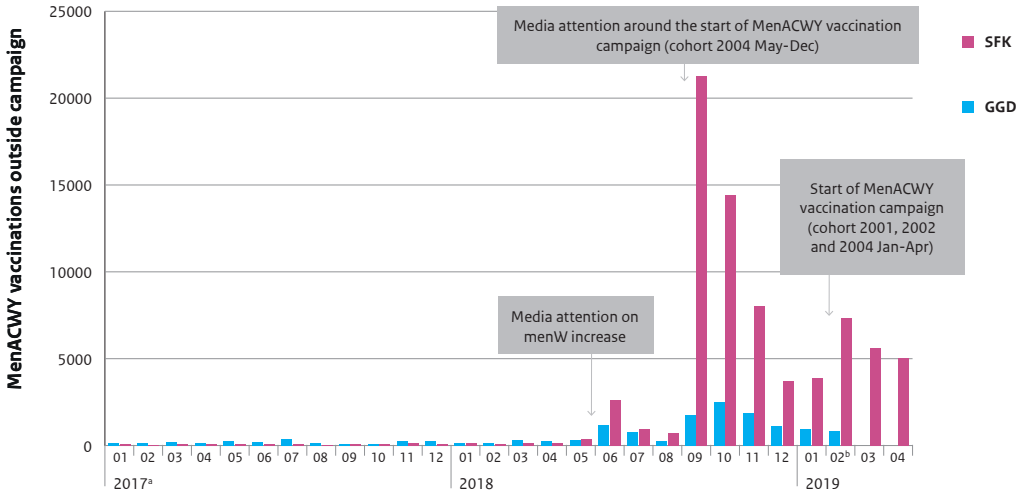

Figure 7.6.7 Number of MenACWY vaccines administered outside the NIP and adolescent vaccination campaigns by GPs and by 15 GGDs per month between 2017 and 2019 in the Netherlands.

a Only 10 of the 15 GGDs provided information on vaccination in 2017

b GGD data was only available up to February

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 has increased since 2015 to an incidence of 1.2 per 100,000 in 2018 and 2019 (data up to June) (Figure 7.6.1). This increase was caused mainly by an increase of serogroup W (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 to 18-year-olds, the number of cases of meningococcal serogroup C (MenC) disease has decreased enormously, from 277 in 2001 to an average of 6 cases per year since 2005 (Figure 7.6.2). The incidence decreased in all age groups due to herd protection, and has remained lower than 0.1 per 100,000 since 2005 (Figure 7.6.1).

In 2018, only 1% of all meningococcal cases were serogroup C. Three cases of MenC were reported, all between 45-64 years of age (Figure 7.6.3). Up to June 2019, five MenC cases were reported (Figure 7.6.3). There were no vaccine failures in 2018 and 2019. Since the introduction of the conjugated MenC vaccine in 2002, there have been five vaccine failures. Two of these patients had an underlying immune deficiency. None of the MenC cases in 2018 and 2019 died. Since 2015, one MenC case has died resulting in a case fatality rate of 3% (1/31).

7.6.3.3 *Meningococcal serogroup W*

Since May 2018, MenACWY vaccination at 14 months of age is part of the national immunisation programme. In October and November 2018, children born between 1 May and 31 December 2004 were offered MenACWY vaccination. The vaccination uptake in this cohort was 87%. From March to June 2019, all children born between 1 January 2001 and 30 April 2004 were offered MenACWY vaccination in a one-off catch-p campaign. Preliminary vaccination uptake was 81% in this catch-up campaign. From 2019 onwards, MenACWY vaccination is offered to children in the year they turn 14 years as part of the national immunisation programme.

The incidence of MenW disease has been rising since 2015, with an incidence of 0.47 per 100,000 in 2017 (n=80) and 0.60 per 100,000 in 2018 (n=103) (Figures 7.6.1 and 7.6.2). In 2018, 50% of all meningococcal cases were serogroup W and more MenW than MenB cases were reported. In the first six months of 2019, the incidence of MenW decreased to 0.45 per 100,000 (n=39).

The increase in MenW disease was observed in all age groups, with the highest incidence in <2-year-olds, 14- to 18-year-olds, and >80-year-olds (Figure 7.6.4). In the first six months of 2019, a decrease or stabilisation of the incidence was seen in all age groups, except >80-year-olds. There have been no MenW cases, either vaccinated or unvaccinated, in the cohorts eligible for MenACWY vaccination since its implementation. Whether the decrease or stabilisation of the incidence in other age groups is due to implementation of MenACWY vaccination is difficult to say. It seems too soon after implementation of MenACWY vaccination in adolescents to observe a vaccine effect in groups not eligible for vaccination at this time already.

Since 2015, 45 out of 274 (16%) MenW cases have died, with 23 deaths reported in 2018. Deaths occurred in nearly all age groups, with the highest case fatality rate in 14- to24-year-olds (15/58=26%).

7.6.3.4 *Meningococcal serogroup B*

The incidence of meningococcal serogroup B (MenB) disease has been declining steadily since the late nineties and has stabilised at 0.5 per 100,000 since 2011 (Figure 7.6.1). In 2018, 36% of all meningococcal cases were serogroup B. In total, 74 cases of MenB disease were reported (Figure 7.6.2), showing a slight increase since 2014. Up to June 2019, 41 MenB cases were reported, similar to the same period in 2018 (n=47). The incidence of MenB disease in 2018 was highest in children aged under five(3.6 per 100,000, n=31) and 2019 (3.7 per 100,000, n=16 up to June), followed by 15- to 24-year-olds with an incidence of 0.7 per 100,000 (n=15) in 2018 and 1.0 per 100,000 (n=11) up to June 2019 (Figure 7.6.5).

Since 2015, 17 out of the 330 (5%) MenB cases have died. Case fatality rates are rather similar between age groups. In the last five years, 1-2 children under 5 years of age died of MenB disease each year.

7.6.3.5 *Meningococcal serogroup Y*

The incidence of meningococcal serogroup Y (MenY) disease has increased slightly over the last 2-3 years with an incidence of 0.14 per 100,000 in 2018 (n=24) and 2019 (n=11 up to June) (Figure 7.6.1 and 7.6.2). In 2018, 12% of all meningococcal cases were serogroup Y. Most cases

were adults aged 45 years or older (16/24 in 2018 and 8/11 in 2019). Since 2015, 5 out of 80 (6%) MenY cases have died.

7.6.3.6 Other meningococcal serogroups

In 2018 and 2019, two cases of meningococcal disease due to a non-groupable meningococcus were reported (Figure 7.6.2).

7.6.4 Pathogen

In 2018 and 2019, two adult MenC cases were reported with finetype P1.5-1,10-8:F3-6, the finetype that recently caused an outbreak in Tuscany, Italy. This finetype is also associated with several outbreaks among MSM in past years in various countries.

Almost all serogroup W strains from 2015 to 2018 had the same finetype P1.5,2:F1–1 (210/234; 90%) and belonged to clonal complex 11 (cc11; 209/224; 93%). Cluster analysis of all available genome sequences of serogroup W cc11 meningococci isolated in 2012-2018 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, several separate clusters can be discerned within the same year, suggesting different introductions or, more likely, expansions of subclones.

Since 2016, an increase was observed in the number of MenB cases with finetype P1.22,14:F5-1, which caused three MenB cases in 2016, twelve in 2017, seven in 2018, and eight up to June 2019. Before 2016, this finetype was only detected in one MenB case in 2009 and two cases in 2014. Whole genome sequencing showed that almost all of the B:P1.22,14:F5-1 belonged to cc32. Of 29 B:P1.22,14:F5-1 cases since 2016, 12 lived in GGD region Rotterdam Rijnmond and an additional seven cases lived in other GGD regions in the south-west of the Netherlands. Most cases (15/29; 52%) were 10-19 years of age and two cases died (7%). All B:P1.22,14:cc32 isolates were potentially covered by the 4CMenB vaccine (Bexsero) because of an exact match with one of the antigens in the vaccine.

In 2017 and 2018, 351 out of 379 received meningococcal isolates were assessed by whole genome sequencing. As described above, the vast majority of serogroup W isolates belonged to cc11 (95%). Among serogroup Y, cc23 was the dominant clonal complex (75%). Serogroup B isolates consisted of 11 different clonal complexes, with 80% of assigned isolates belonging to cc32 (33%), cc41/44 (21%), cc269 (13%), or cc213 (13%). Among 11 serogroup C isolates, most belonged to cc11 (64%).

7.6.5 Research

The potential vaccine coverage of the 4CMenB vaccine (Bexsero) for Dutch meningococcal disease isolated in 2017 and 2018 was estimated using the phenotyping tool of the Bacterial Isolate Genome Sequence Database (BIGSdb) at PubMLST.org/Neisseria. For serogroup B, 73/108 (68%) isolates were potentially covered by 4CMenB. Coverage was highest among 5- to24-year-olds (88%), while that among 0- to 4-year-olds was 59%. Of serogroup W isolates, 155/161 (96%) were predicted to be covered by 4CMenB, while only 2/42 (5%) of serogroup Y

isolates were potentially covered. The phenotyping tool that was used is based on association with MATS, which may underestimate coverage.

The feasibility of saliva sampling in detecting carriage of *N. meningitidis* was tested in young adults, the age group at elevated risk of invasive meningococcal disease and also considered to be the main reservoir of meningococci in the population. Saliva samples along with standard oropharyngeal (OP) swabs were collected from 150 students of the University of Applied Sciences Utrecht, all presumably vaccinated with MenC vaccine. Presence of meningococci was detected with conventional diagnostic culture and with qPCR. Altogether, 53 (35% of a total of 150) students were identified as carriers of meningococci. Out of 41 (27% of 150) culture-confirmed carriers of meningococci, 37 (25% of 150) were positive in OP swabs and 27 (19% of 150) in saliva. With a concordance of 89%, the difference between OP versus saliva cultures was not significant (McNemar's, p=0. 08). Out of the 53 students identified as carriers of meningococci with qPCR, 47 (31% of 150) were positive in OP swabs and 39 (27% of 150) in saliva. The difference between qPCR results for OP swabs and saliva was also not significant (McNemar's, p=0.12) with a concordance of 87%. The oropharyngeal sample was not clearly superior over saliva in any of the circumstances tested in detecting carriage of *N. meningitidis* in young adults. *N. meningitidis* isolates cultured from OP swabs were serogrouped by qPCR and yielded 12 menB (32% of 37), 2 menC (5% of 37), 2 menW (5% of 37), and 11 menY (30% of 37) isolates. As it is easier to collect saliva than OP swabs, collecting saliva could be considered in future surveillance of meningococcal carriage.

After the incidence of menW disease started rising, a higher demand for MenACWY vaccination emerged in the Netherlands. People were advised to consult the Dutch Municipal Health Service (GGD) or their general practitioner (GP) if they wanted to be vaccinated although they had to pay for the vaccination. To gain insight into the number of persons vaccinated outside the NIP and adolescent vaccination campaigns, data from the GGDs and the Dutch Foundation for Pharmaceutical Statistics (SFK) were analysed. Data from 15 of the 25 GGDs in the Netherlands were included in the analyses, since they provided information on vaccination date. The GGDs included in the study cover 61% of the Dutch population. The SFK data include information on the number of vaccines dispensed in each month by year of birth of the purchaser from nearly all public pharmacies in the Netherlands. Although these records do not necessarily imply that the vaccine has been administered, we assume that they were actually administered by the GPs.
In 2018, 52,617 MenACWY vaccines were administered by GPs and 10,628 by 15 GGDs, substantially more than in 2017 (SFK: n= 1,073; 10 GGDs: n = 2,245) (Figure 7.6.7). The first increase in MenACWY vaccinations occurred in June 2018. However, the greatest numbers were observed from September to November 2018. From all MenACWY vaccines administered by GPs and 11 GGDs in 2018 and 2019, 8% were administered to children <4 years, 22% to 4- to 8-year-olds, 17% to 9- to 13-year-olds, 22% to 14- to 18-year-olds, 18% to 19- to 23-year-olds, and 13% to persons ≥24 years.
Within the cohorts eligible for vaccination in the adolescent vaccination campaigns in the fall of 2018 and spring of 2019, vaccination coverage outside the NIP was estimated at 1.9% (11 GGDs: 1,423/ 428,437 [0.3%]; SFK: 16,384 / 100,5631 [1.6%]) among children born between 2001

and 2005, and at 0.09% (11 GGDs: 50/55,882) among children born between May and December 2004.

7.6.6 (Inter)national developments

7.6.6.1 Health Council recommendation

In December 2018, the Health Council of the Netherlands recommended implementing the MenACWY vaccination in the national immunisation programme for 14-year-olds and continuing MenACWY vaccination at 14 months of age [3]. The Health Council did not recommend adding the MenB vaccination to the national immunisation programme because of uncertainty concerning the vaccine's effectiveness and because the vaccine can cause high fever, especially in infants and when administered simultaneously with other routine vaccines. In addition, the cost-effectiveness of MenB vaccination is highly unfavourable compared to the commonly used reference value of €20,000 per quality adjusted life year. The Council advised reconsidering the recommendation when new data on effectiveness become available.

7.6.6.2 Carriage

Peterson et al. performed a review and meta-analysis to estimate serogroup-specific meningococcal carriage by age group and world region [4]. Data of fourteen studies from European countries were included, among which one Dutch study. Carriage rates were higher in 18- to 24-year-olds compared with 11- to 17-year-olds. Carriage of serogroup A, C, W and X was <1% in both age groups. Carriage of serogroup B was 1.9% in 11-to 17-year-olds and 5.0% in 18- to 24-year-olds, while carriage of serogroup Y was <1% in 11- to 17-year-olds and 3.9% in 18- to 24-year-olds. In general, carriage patterns by age were similar across serogroups within a region but varied between regions.

7.6.6.3 Meningococcal disease

Wang et al. performed a systematic review and meta-analysis to assess case fatality rates (CFR) by serogroup and age [5]. The authors included 40 studies published between January 2000 and May 2018. The pooled CFR was 8.3%. Serogroup B was associated with a lower pooled CFR (6.9%) than other serogroups (W: 12.8%, C: 12.0%, Y: 10.8%). The CFR was 9.0% in infants, gradually decreased to 7.0% in 7-year-olds, subsequently increased to 15.0% in young adults aged 28 years, stabilised between 15 to 20% in middle-aged adults, and then increased with age up to 40%.

Pregnancy is associated with an immunocompromised state and pregnant women are at significantly higher risk of certain severe infections compared to non-pregnant women. Parikh et al investigated whether pregnant women are also at increased risk of invasive meningococcal disease (IMD) [6]. From 2011 to 2014, 310 IMD cases in women of reproductive age were reported, including four who were pregnant at IMD confirmation. All four cases survived; one case in the first trimester had a septic abortion. The incidence of IMD was lower in pregnant than in non-pregnant women (relative risk: 0.21, 95% CI: 0.06-0.54).

7.6.6.4 MenB disease

Soeters et al reviewed university-based outbreaks of meningococcal disease caused by serogroup B and vaccination responses in the United States in the years following MenB vaccine availability [7]. Ten university-based outbreaks occurred in 7 states during 2013–2018, causing a total of 39 cases and 2 deaths. Outbreak case counts ranged from 2 to 9 cases; outbreak duration ranged from 0 to 376 days. All 10 universities implemented MenB vaccination: 3 primarily used MenB-FHbp and 7 used 4CMenB. Estimated first-dose vaccination coverage ranged from 14% to 98%. In 5 outbreaks, additional cases occurred 6–259 days following MenB vaccination initiation. The authors conclude that although it is difficult to predict outbreak trajectories and assess the effects of public health response measures, achieving high MenB vaccination coverage is vital in helping to protect at-risk persons during outbreaks of meningococcal disease caused by this serogroup.

Stefanelli et al described an outbreak of five MenB cases between 1 January and 31 March 2018 on the Italian island of Sardinia [8]. Disease was caused by a B:P1.5-1,10-8:F3-6:ST-11(cc11) strain, which probably emerged after capsule switch of a C:cc11 strain. The cases were 18-21 years old and two of the cases died. All patients had attended the same nightclub in the two weeks prior to symptom onset. Capsular switching from MenC to MenB among cc11 meningococci is of concern due to high disease severity. Capsule switching has occurred before within cc11 meningococci and other MenB:cc11 outbreaks have also been reported.

In 2014, a vaccination campaign with the 4CMenB vaccine was carried out among all persons ≤20 years in the Saguenay-Lac-Stain-Jean region in Quebec, Canada, because of a long-lasting outbreak caused by a ST-269 serogroup B strain. Deceuninck et al reported on the impact of this mass vaccination programme four years after its implementation [9]. In all, 83% of the population ≤20 years in the Saguenay-Lac-Stain-Jean region was vaccinated. In persons ≤20 years, the incidence decreased from 11.3 per 100,000 in July 2006-June 2014 (56 cases) to 0.44 per 100,000 in July 2014-June 2018 (1 case), a reduction of 96%. In other regions in Quebec the incidence also decreased but to a much lower extent (58% reduction). In persons >20 years, the incidence decreased by 59% in the Saguenay-Lac-Stain-Jean region in Quebec and by 56% in other regions, suggesting no herd effect among unvaccinated older adults. From July 2014-June 2018 and among persons targeted by the campaign, the incidence of IMD-B was 0.51 per 100,000 in vaccinated (1 case) and 2.45 per 100,000 in unvaccinated persons (1 case), resulting in an estimate of direct vaccine protection of 79% (95%CI: -231 to 99%).

7.6.6.5 MenC disease

In 2015-2016, an outbreak of MenC:P1.5-1,10-8:F3-6:ST11(cc11) was reported in Tuscany, Italy, with 62 cases of MenC and 17 clusters [10]. Further investigation of the Tuscany outbreak showed that six discos and four gay venues were transmission hotspots, having been attended by 20 and 14 cases respectively in the 10 days before onset of symptoms. Cases occurred among men who have sex with men (MSM) and bisexual individuals, as well as heterosexuals attending gay venues. Molecular typing indicated a close relationship with MenC clusters recently described among gay, bisexual and other MSM in Europe and the United States, suggesting a possible international spread of the serogroup C variant P1.5–1,10–8:F3–6:ST-

11(cc11) in this population group; however, epidemiological links were not identified. A reactive vaccination campaign targeting all residents of Tuscany was implemented in May 2015. A targeted vaccination campaign involving night clubs and lesbian, gay, bisexual, and transgender associations was implemented in December 2016. In the course of 2017, 10 cases of MenC occurred, suggesting the effectiveness of the reactive and targeted immunisation programmes.

Pezzotti et al described MenC vaccine failures and estimated vaccine effectiveness during the MenC outbreak in Tuscany, Italy [11]. Of 61 MenC cases in 2015 and 2016, 12 were vaccinated. The time interval from immunisation to IMD onset was 20 days in one case, from 9 months to 3 years in six cases and 7 years or more in five cases. Estimated vaccine effectiveness was 77% (95% CI: 36-92) during the outbreak.

7.6.6.6 MenW disease

Krone et al described the rise of MenW disease in Europe using data of 13 European countries from 2013 to 2017 [12]. MenW incidence increased significantly from 0.03 per 100,000 in 2013 to 0.11 per 100,000 in 2017. Significant increases in MenW incidence were seen in England, Germany, Spain, the Netherlands, Sweden, Switzerland, and Norway. The Netherlands, England, Switzerland, and Sweden had the highest MenW incidence in 2017, ranging from 0.17 per 100,000 in Sweden to 0.47 per 100,000 in the Netherlands. Of the culture-confirmed MenW cases, 80% were caused by cc11.

7.6.6.7 Cost-effectiveness

Leeds et al assessed the cost-effectiveness of recently registered vaccines for universal vaccination [13]. Costs and benefits of universal vaccination at college entry were estimated from both a health sector perspective and a societal perspective. The incremental cost per quality-adjusted life year gained with universal vaccination was $13.9 million from the health sector perspective and $13.8 million from the societal perspective. The authors concluded that universal vaccination at college entry is not cost-effective. The low incidence of MenB disease and high vaccine costs contribute to the cost-ineffectiveness of universal vaccination.

7.6.7 Literature

7.6.7.1 References

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7.6.7.2 Other recent RIVM publications

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7.7 Mumps

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7.7.1 Key points

- The incidence of mumps in 2018 was low (0.4 per 100,000), but higher than the previous year.
- Most of the mumps cases in the Netherlands were caused by mumps virus genotype G.
- A third dose of MMR vaccine increases immune protection in young adults and could be considered as an intervention in controlling a mumps outbreak.

7.7.2 Tables and figures

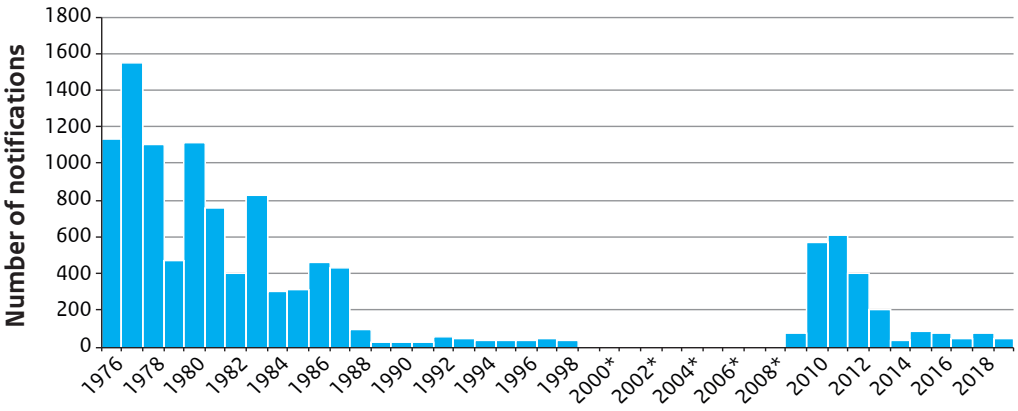

Figure 7.7.1 Number of notified mumps cases in the period 1976-2019
* In the period 1999-2008 mumps was not notifiable
Year 2019: up to 1 May
Source: Osiris

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. From late 2009 until 2012, a countrywide epidemic with over 1,500 reported cases occurred that especially affected (vaccinated) student populations (Figure 7.7.1) [1]. Since 2012, the number of reported mumps cases among students has declined in the Netherlands.

In 2018, 73 cases of mumps were reported (Figure 7.7.1). Almost as many males (n=38) as females (n=35) were reported, with a mean age of 29 years (range 3-82). Fifty cases were

vaccinated; 6 (12%) with one dose, 41 (82%) with 2 doses, and 3 (6%) with 3 or more doses of vaccine. On average, the 17 unvaccinated cases were 41 years old (range 5-82). The vaccination status was unknown for the 6 remaining cases. A minority of these cases (n=13) was imported or likely to be imported. Of these patients, 2 were hospitalised and 2 adults reported orchitis.

In 2018, 5 clusters were identified. The first cluster occurred in an asylum seekers' centre and involved 6 people from Cuba aged between 21 and 36 years with mumps. The source of infection had possibly been abroad or in the holding facility where they stayed after arrival. Another 3 small clusters consisted of 2 or 3 patients who were partners or family members. The last cluster consisted of 14 students and 3 close contacts reported between October and November 2018. Most of the students were in their early twenties and part of the transmission was related to a student association. Cases from the last 4 clusters were most probably infected in the Netherlands.

Up to 1 May 2019, 42 mumps cases have been reported. There were more male (67%) than female patients and the mean age was 27 years (range 3-60). In all, 19 students were reported and 4 acquired the infection abroad. Most cases (n=30, 71%) were sporadic mumps cases, except for 2 clusters. The first cluster of 4 patients was reported in February 2019 and included 2 students. The second cluster included 8 students from 3 different student houses in the same city.

7.7.4 Pathogen

Since 2010, most of the mumps cases in the Netherlands have been caused by mumps virus genotype G. In 2018 and the first 4 months of 2019, 61 cases (53%) were genotyped. The majority (89%) of these cases was genotype G, of which most were genetically identical based on sequencing of the small hydrophobic gene region. In addition, 3 other genotypes were detected in a small amount of cases: genotype C (3 cases), H (1 case) and K (3 cases). Many cases with non-G genotypes were imported cases from various countries in Asia and Africa, were these mumps serotypes are currently circulating [2].

7.7.5 Research

RIVM performs multi-disciplinary research to gain insight into the cause of, and establish possible solutions for, the occurrence of mumps outbreaks among young vaccinated adults.

7.7.5.1 Surveillance

7.7.5.1.1 Molecular surveillance

Currently, molecular surveillance worldwide focuses primarily on sequencing of the small hydrophobic gene and adjacent non-coding regions (SH; 316 nucleotides). However, some studies have highlighted the importance of obtaining additional sequence information by showing that additional genes or regions contribute to the resolution of the sequence data, in such a way that mumps cases that seem to be linked to the same source on the basis of the SH sequence appear to be linked to another source or chain of transmission [3-5]. In 2018, sequence data from various regions of mumps viruses were obtained from cases in the Netherlands reported between 2010 and 2018, aiming to elucidate to what extent sequencing additional regions provided sufficient information for molecular surveillance. Results of this

study indicate that the non-coding regions (NCRs) sequencing data provided similar or slightly better sequence resolution compared to the HN and F genes for most viruses. For molecular surveillance of currently circulating mumps genotype G viruses, sequencing of SH in combination with NCRs is a useful approach [6]. Analysis of NCR sequence data from mumps viruses with identical SH sequence detected in four epidemiological clusters in 2018-2019 showed some variation and made it possible to genetically distinguish the mumps viruses from the different clusters.

7.7.5.1.2 *Visual tool*

With a growing amount of different types of data (e.g. geographical data, time, genetic sequence) becoming available in routine surveillance, the identification of clusters of persons linked to each other by transmission relies increasingly on automated algorithms. In 2019, visual tools were developed in order to identify transmission clusters and applied to mumps surveillance data from January 2009 to June 2016. In this period, five clusters were identified of which three were defined as plausible, one as questionable, and one as implausible. Comparison with the clusters reported by the Netherlands Early Warning Committee showed that the plausible and questionable clusters were indeed reported as clusters while the implausible cluster was not. These tools can help outbreak investigators focus on the most plausible clusters [7].

7.7.5.2 *Cellular immunity*

Mumps outbreaks among vaccinated young adults stress the need for a better understanding of mumps virus-induced immunity. Mumps-specific antibodies, especially virus neutralising antibodies, have been implicated in immune protection but correlation is still poor, while studies on T cell responses are limited. Nevertheless, it is evident that both CD8+ and CD4+ T cells are important in the defence against viral infections. We recently identified the first conserved CD4+ T cell epitope involved in mumps immunity, which we found in all tested mumps patients sampled in a clinical cohort during the last mumps outbreak in the Netherlands (2011-2012). This provides a broadly applicable tool to study the role of virus-specific T cell responses upon mumps virus infection or vaccination [8].

7.7.5.3 *Clinical MMR-3 study*

A clinical study was performed (2016-2018) to investigate whether a third dose of the measles, mumps and rubella (MMR-3) vaccine may help protect young adults at risk during a mumps outbreak [9, 10]. The study included 147 vaccinated participants between 18 and 25 years of age. Upon third-dose vaccination, antibody responses for most participants were boosted to above the cut-off level for immune protection up to one year after vaccination. This protective cut-off level was modelled from a Dutch cohort of mumps virus-infected persons from which pre-mumps antibody levels were derived. This indicates that the immune protection from a third dose of MMR lasts longer than previously assumed based on another MMR-3 study from the US reported by Fiebelkorn et al [11].
MMR-3 vaccination is therefore expected to be an effective intervention for controlling mumps outbreaks. A follow-up study to determine the immunogenicity up to three years post-MMR-3 vaccination will start at the end of 2019.

7.7.6 International developments

In 2018, in response to numerous mumps outbreaks reported throughout the United States, the Advisory Committee on Immunization Practices (ACIP) recommended a third dose of measles, mumps, and rubella (MMR) vaccine for groups of persons determined by public health authorities to be at increased risk of acquiring mumps because of an outbreak [12]. The CDC recently published guidelines for the implementation of this recommendation with a set of tools including a decision matrix to determine increased risk, as well as tables to classify the evidence of transmission in the setting and determine the likelihood of transmission. A list of additional factors to consider beyond evaluating transmission in the setting is also provided. The guidelines provide a framework to assist public health authorities in identifying specific risk groups prior to or during outbreaks that are eligible for a third dose of MMR vaccine [13].

7.7.7 Literature

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*RIVM publication

7.8 Pertussis

J. Fröberg, A. Buisman, G.A.M. Berbers, N. Rots, A.W.M. Suijkerbuijk, C.A.C.M van Els, H.E. de Melker, R. Mariman, N.A.T. van der Maas

7.8.1 Key points

- In 2018, the incidence rate (IR) of pertussis was 28.5 per 100,000, compared with 28.7 per 100,000 in 2017.
- In 2019 up to 1 May, a rise in pertussis notifications was observed (IR of 38.8), fitting the epidemiological peak pattern of 3-5 years in countries with high vaccination coverage. The incidence rate was highest in children below six months of age.
- The prevalence of prn-deficient strains in the Netherlands rose sharply in 2018-2019.
- There is an increase in the number of pregnant women who get a maternal pertussis vaccination, with estimated vaccination coverages of 13% in 2018 and 26% in 2019 up to 1 April.
- Material pertussis vaccine will be offered as part of the NIP in December 2019.

7.8.2 Tables and figures

Figure 7.8.1 Pertussis notifications (left Y-axis) and hospitalisations (right Y-axis) per 100,000 for 1999-2018* Source: OSIRIS, Statistics Netherlands

*Hospitalisation data for 2017 are preliminary. No hospitalisation data for 2018 onwards are available at this time.

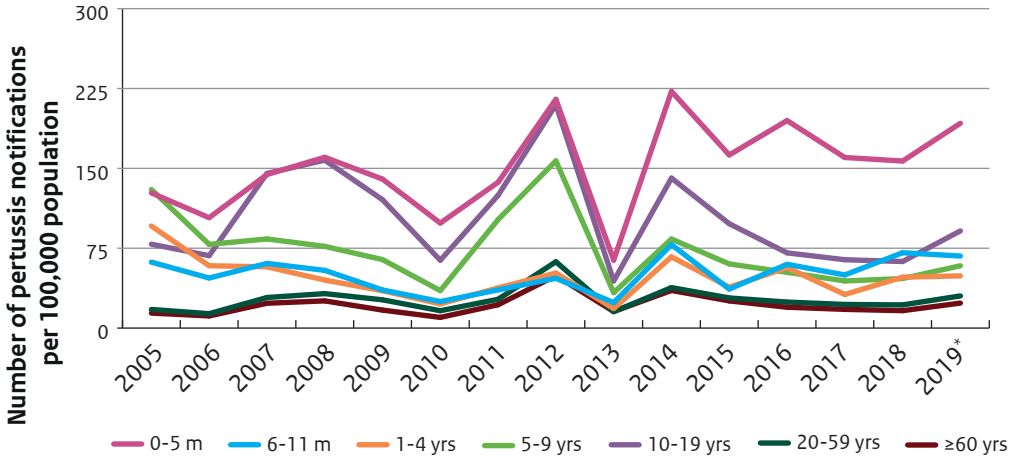

Figure 7.8.2 Pertussis notifications per 100,000 per age group for 2005-2019* Source: OSIRIS
*reports up to 1 May 2019 are included

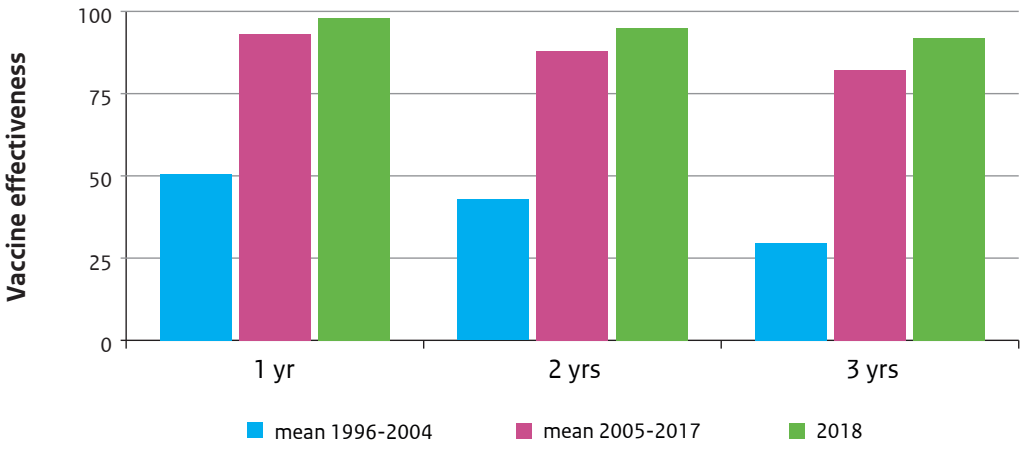

Figure 7.8.3 Vaccine effectiveness of the primary pertussis vaccination, calculated with the screening method*, estimated for 1-, 2-, and 3-year-olds during implementation of the whole-cell pertussis vaccine (mean 1996-2004) and during implementation of the acellular pertussis vaccine (mean 2005-2017, and 2018 separate)
Source: OSIRIS, National vaccination coverage report
*A population coverage of 94% was used for 2017; a coverage of 93% was used for 2018. For all other years, a population coverage of 96% was used.

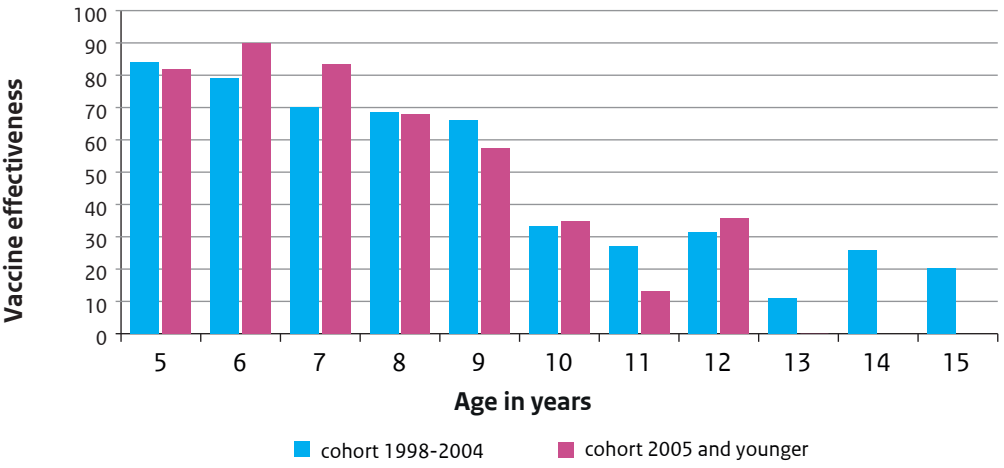

Figure 7.8.4 Mean vaccine effectiveness of the pre-school booster, calculated with the screening method*, estimated for 5- to 15-year-olds for the whole cell pertussis priming cohorts (1998-2004) and the acellular pertussis priming cohorts (2005 and younger). Not all cohorts of 2005 and younger have reached the age of 10-15 years yet.

Source: OSIRIS, National vaccination coverage report

*For all separate birth cohorts, the registered population coverage of the booster vaccination was used as retrieved from the national vaccination coverage report.

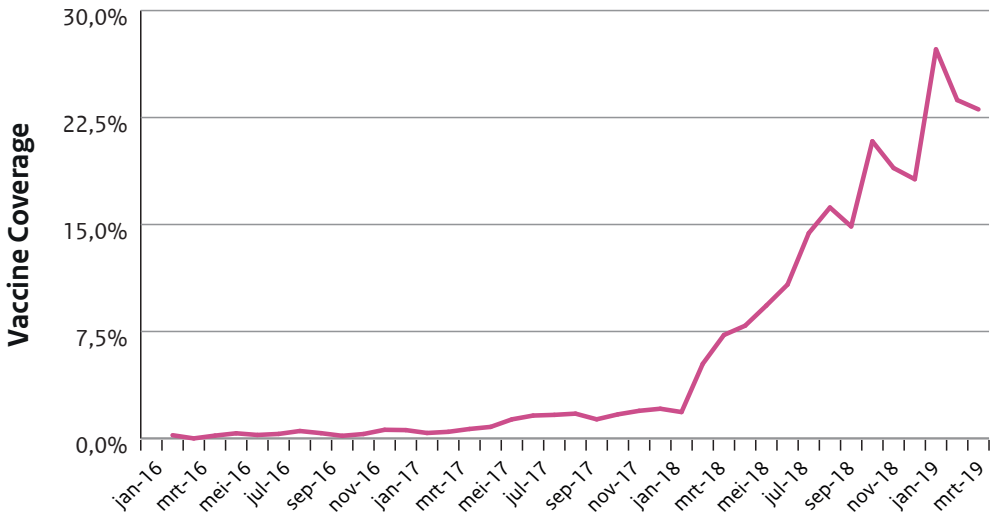

Figure 7.8.5 Estimated vaccine coverage for the maternal pertussis vaccine from 2016 up to 1 April 2019.* For more information, see Appendix 1 on surveillance methodology.

*March only includes SFK data. Aggregated data not included in this graph.

Source: Statistics Netherlands, SFK data, municipal health services

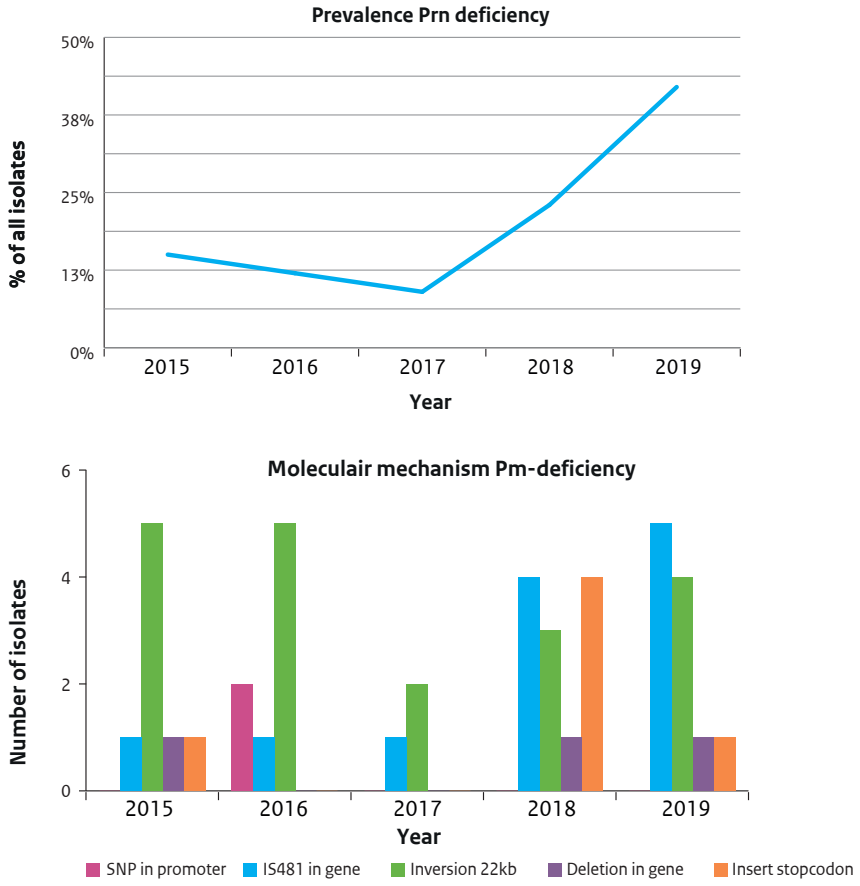

Figure 7.8.6 Prevalence (A) and molecular mechanism (B) of loss of pertactin (Prn) production in clinical isolates collected between 2015 and May 2019

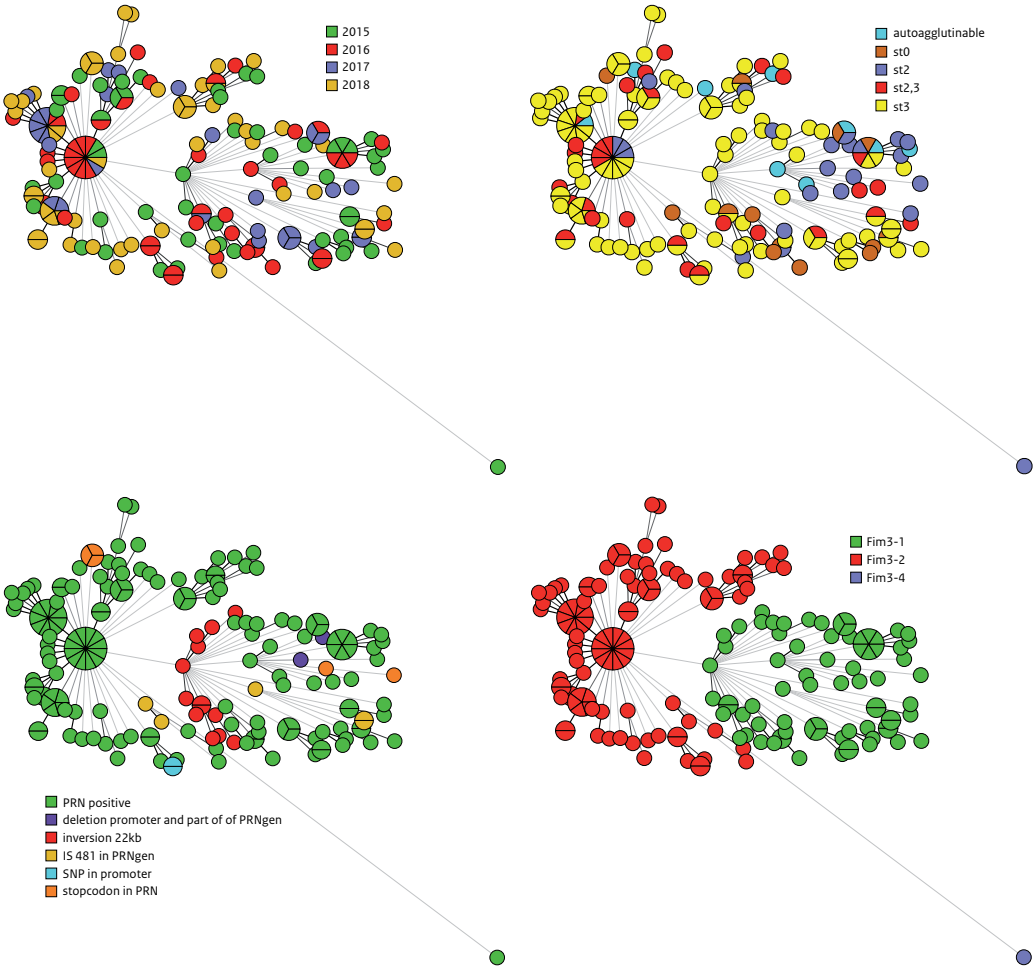

Figure 7.8.7 Genetic relationship between 204 clinical isolates based on wgMLST, with clustering based on year (A) and serotype (B), the genetic relationships between Prn strains by molecular mechanism (C) and Fim3 subtype (D)

7.8.3 Epidemiology

7.8.3.1 Disease

In 2018, the overall incidence rate (IR) of pertussis notifications was similar to 2017 and somewhat lower than 2016 (28.5 per 100,000 vs 28.7 and 32.6 per 100,000 in 2017 and 2016). In 2019 up to 1 May, the IR was 38.8 (Figure 7.8.1). The last epidemic peak in pertussis notifications was seen in 2014/2015, so an epidemiological rise in pertussis notifications in 2019 would be in line with expectations, with a peak pattern of 3-5 years in countries with a high vaccination coverage. Hospitalisation data for 2018 are not yet available.
For the age categories 6-11 months and 1-4 years, the IR increased in 2018 compared to 2017.

The IR for 0- to 5-month-olds and 10- to 19-year-olds decreased slightly in 2018, continuing the downward trend from 2014 onwards. The IR of other age groups remained stable. Looking at the first trimester of 2019 (1 January – 1 May), we see an increased IR for all age categories, except the 6- to 11-month-olds. (Figure 7.8.2). This increase is most obvious in the 0- to 5-month-olds and 10-to 19-year-olds. In the 0-to 5-month-olds, the IR increased from 157 cases per 100,000 in 2018 to 192 per 100,000 in 2019 up to 1 May. In 10- to 19-year-olds, the IR increased from 63 cases per 100,000 to 91 per 100,000. The observed rise of pertussis notifications in all age groups supports the possibility of 2019 becoming an epidemic year, as this was also seen in previous epidemic years.
One pertussis-related death was notified in 2018, a 0-year-old who was too young to be vaccinated. In the beginning of 2019, another death of an infant girl too young to be vaccinated was notified. In addition, an unvaccinated 88-year-old woman was reported to have died due to pertussis.

7.8.3.2 Vaccine effectiveness (VE)

Figure 7.8.3 shows the VE calculated with the 'screening method' for the infant vaccination series. The VE presented here should not be interpreted as the 'true' absolute estimate of the effectiveness. It is merely a way to study the trend in VE estimations. Since the switch from whole-cell pertussis vaccine to an infant-combination vaccine with an acellular pertussis component, the VE has been continuously high up to the booster vaccination given at 4 years old. However, after the booster dose at 4 years of age the VE shows a decrease after ~5 years, i.e. when children reach the age of 10 years, (Figure 7.8.4). This is in line with the notification rates for these age groups, as the 10- to 19-year-olds have a higher IR compared to the 1- to 9-year-olds. Please note that the reported VE differs from the VE reported in our previous reports. This is due to a change in the way the VE is calculated. We have now used the reported vaccination coverage for each birth cohort separately to account for the recent change in vaccination coverage. For more information, see Appendix 1 on surveillance methodology.

7.8.3.3 Maternal pertussis vaccination coverage

Pregnant women are able to get a maternal pertussis vaccination, but have to pay for the vaccination as it is not yet implemented as part of the NIP. Implementation within the NIP is scheduled for December 2019.
Vaccination data for women in the fertile age group (20-45 years) were collected from the national apothecaries (SFK) and municipal health services, and analysed to generate an estimate of the maternal pertussis vaccination coverage. The number of pregnant women in 2017 was obtained from Perined (numbers for 2018 and 2019 were not yet available). An approximate baseline number of vaccinations was subtracted from the total number of vaccinations. This baseline consisted of three approximate numbers: 1. Vaccinations administered before the maternal vaccination was available; 2. Vaccinations related to travel; 3. Vaccinations related to healthcare professions. Note that the resulting vaccination coverage is a rough estimate. For a detailed description of the methodology, please refer to Appendix 1 on surveillance methodology.
Figure 7.8.5 shows the estimated vaccine coverage of the maternal pertussis vaccination for 2016-2018. Starting early in 2018, there has been an increase in the administration of pertussis

vaccine to women 20-45 years of age. The average vaccine coverage in 2018 was 13% (N= 21,845). In 2019 up to 1 April, the number of vaccinations administered continued to rise, with an estimated average vaccine coverage of 26% (N= 10,902). Although these results are not precise enough to draw conclusions, they show that more attention is devoted to the maternal pertussis vaccination since women are actively seeking vaccination.

7.8.4 Pathogen

To study the possible adaptions of the bacteria, Dutch medical microbiology laboratories are requested to submit their *B. pertussis* suspected samples to the RIVM. Strain surveillance focuses on changes in the genotype and phenotype of the *B. pertussis* family in the Netherlands. Confirmed *B. pertussis* strains are whole genome sequenced (WGS) and an antigen expression validation assay is performed for the pertussis antigens: pertussis toxin (Ptx), pertactin (Prn), and filamentous hemagglutinin (FHA).
Although *B. pertussis* was confirmed by molecular diagnostics methods in almost all submitted samples, a single Bordetella colony cannot always be obtained due to lack of viability or polymicrobial overgrowth. In 2018, a Bordetella species could be culture-confirmed in 56 out of 248 (23%) submitted samples, 53 of which were *B. pertussis*. Other species identified were *B. holmesii* (n=2) and *B. parapertussis* (n=1). Compared to 2017, RIVM largely extended its network of participating laboratories resulting in a more than twofold increase in received samples as compared to 2017. In 2018, Bordetella suspected specimens were obtained from 19 different medical microbiology laboratories, however ~50% of all isolates were derived from only four sites. The aim is to increase the number of contributing laboratories further in order to achieve complete geographical coverage of the Netherlands.

In the Netherlands, the NIP uses an acellular pertussis vaccine consisting of three pertussis antigens, namely Ptx, FHA and Prn. The re-emergence of pertussis has been attributed to several factors including bacterial strain adaptation due to vaccine pressure [1]. Therefore, carefully monitoring the expression of vaccine targets, in particular Prn, by the bacteria is vital. A high frequency of Prn- or FHA-deficient *B. pertussis* isolates could be prognostic of vaccine evasion, leading to a greater number of pertussis cases.
Between 2010 and 2015, an emergence of *B. pertussis* isolates was observed that are deficient in the vaccine component Prn, with a prevalence of 10-15% in 2015 to 2017. In 2018 a sharp increase was observed, however, with Prn deficiency in 24% (11/46) of the clinical isolates. This alarming rise seems to continue in 2019, with Prn deficiency in 42% of all isolates (11/26) collected up to May (Figure 7.8.6A). Sequence analysis showed that an inversion of ~22 Kb in the promotor region was the most frequently found (n = 19) cause of prn deficiency followed by an insertion of the IS481 element in the prn gene (n = 12), and insertion of a stop codon (n=5) as shown in Figure 7.8.6B.
In 2018, one clinical strain was isolated that lacks production of the acellular vaccine immunogen FHA. Results for FHA production in the strains collected in the first half of 2019 are expected in August 2019.

Core-genome whole genome multi locus sequence typing (cgMLST) using an in-house scheme consisting of 3,180 genes based on *B. pertussis* isolate B1917 was used to infer genetic

relationships between the isolates. Figure 7.8.7 shows the genetic relationship between all 204 *B. pertussis* strains isolated between 2015 and 2018. No clustering of isolates based on year (Figure 7.8.7A) or serotype (Figure 7.8.7B) was observed, but distinct Fim3 subtype clusters could be identified (Figure 7.8.7D). This is of interest in view of an observed shift from Fim3-1 to Fim3-2 strains, which comprised 65% of all *B. pertussis* strains in 2016 and 2017, and 76% of all isolates in 2018.

7.8.5 Research

7.8.5.1 Cost-effectiveness

Fernandes et al summarised economic evidence for adolescent and adult pertussis vaccination [2]. Twenty-seven economic evaluations of different strategies with tetanus–diphtheria–acellular pertussis vaccines were identified. The most frequent strategies were booster vaccination for adolescents and adults, followed by cocooning and vaccinating pregnant women. In general, the studies found favourable cost-effectiveness ratios for adolescent and adult vaccination, particularly for adolescent vaccination. Assumptions regarding underreporting correction, herd protection and vaccine coverage were crucial to cost-effectiveness results.

The cost-effectiveness of vaccinating pregnant women in Japan was evaluated [3]. The vaccination coverage was assumed to be 50%. The incremental cost-effectiveness ratio (ICER) of this strategy compared with the current no AMV strategy was calculated at ¥9,149,317/per QALY gained (in Euros 2018: €71,300/QALY). One-way sensitivity analyses identified that the pertussis incidence rate and vaccine costs were the two main key variables to affect the ICER. Robust incidence data was not yet available for this study, as pertussis only became a notifiable disease in Japan in 2018.

7.8.5.2 Immunology

7.8.5.2.1 Maternal pertussis vaccination

The effect of maternal acellular pertussis (Tdap) vaccination on the pertussis antibody responses of infants starting primary vaccination at 3 months old was investigated in an open-label, randomised controlled trial [4]. This study was the primary objective of the MIKI study investigating the effect of maternal pertussis vaccination on infants' immune response on infant vaccinations.

The study found that the geometric mean concentration of pertussis toxin antibodies was significantly higher in infants of mothers who were vaccinated, compared to the non-vaccinated control group, at birth and at the age of 2 and 3 months. After the primary vaccinations, antibody concentrations for pertussis toxin and a selection of other pertussis-related antibodies were significantly lower in the maternal vaccination group. However, the clinical consequences of this difference in antibody concentration are not yet clear.

Based on the data of this study and our report on the effect of maternal vaccination on the other infant vaccines, the Ministry of Health, Welfare and Sport decided to change the primary infant immunisation schedule from a 2-3-4-11 to a 3-5-11 months of age schedule when the mother has been vaccinated against pertussis during pregnancy [5, 6]. Exceptions are made for premature children (gestational age <37 weeks), children whose mother is hepatitis B-positive, children whose mother was vaccinated less than two weeks before giving birth, and children of

immunocompromised mothers. These four groups will receive the pertussis vaccination following the 2-3-5-11 months of age schedule.

7.8.5.2.2 Cellular B. pertussis specific immunity

Despite vaccination, pertussis remains an endemic disease that is difficult to control due to strain adaptation and waning immunity. New insights are that primary vaccine type and programming of innate and specific immune cells determine the effectiveness of vaccine-induced immunity. RIVM has contributed to unravelling mechanisms and concepts in collaboration with various universities and Intravacc (Bilthoven). [7-13] A immunoassay was developed to measure the function of *B. pertussis*–specific antibodies. When evaluating antibody responses to this pathogen, it is recommended to consider not only the levels, but also other antibody parameters such as avidity and opsonophagocytosis [8]. To escape host immunity *B. pertussis* has developed different strategies, such as no longer expressing vaccine components or expressing virulence factors that modulate the host's immune response. The effects on the innate immune response of emerging *B. pertussis* strains that no longer express pertactin [11], as well as a novel immunomodulatory property of one of these bacterium molecules, have been documented [9]. These findings highlight the importance of monitoring the emergence of *B. pertussis* strains as well as their effect on the immune response.

7.8.6 International developments

Within the framework of the EUPertstrain group, a partnership of European experts on whooping cough, the organisation of a seroprevalence study in European countries for pertussis and diphtheria in the age group 40-60 years is led by the RIVM and funded by ECDC. At the moment, 18 countries have completed the collection of and shipped the requested sera (around 500) to the RIVM. Measurement of the antibody levels against Pertussis toxin (PT), Diphtheria toxoid (DT) and Tetanus toxin (TT) with the multiplex assay using Luminex technology in all these samples (around 10,000) was completed in April 2019. The final database of around 30,000 results has now been established. The percentages of participants who were most likely recently infected with *B. pertussis* (IgG-PT>100 IU/ml) vary between 2% (Finland) and 9% (Norway), with 13 countries between 4% and 6% suggesting that the pertussis incidence and epidemiological situation for most of the participating countries across Europe is rather similar.

For diphtheria, the prevalence of protective levels of anti-DT IgG antibodies seems quite alarming all over Europe with proportions of participants with DT levels <0.01 IU/ml varying between 4% (Finland) and 43% (Greece). For the more reliable protective level of 0.1 IU/ml, these percentages vary from 23% for Finland up to around 80% for Greece, Ireland, Romania, and the UK. In contrast, the situation for tetanus is very reassuring with only very few participants having anti-TT IgG antibody levels <0.01 IU/ml. In all countries more than 90% of the participants possess protective anti-tetanus antibody levels >0.1 IU/ml, except for Greece and Ireland (79-83%).

The periscope consortium, consisting of pertussis experts from 2 vaccine companies, 4 national institutes including the RIVM, and 16 European universities, is working on an extensive IMI-2 project. The main objective of this project is to unravel the difference in protective properties between the aP vaccines, the wP vaccines, and natural infection, and to

characterise new biomarkers for pertussis immunity. The consortium described its views on how to move forward towards effective control of pertussis in a high-impact review paper that was published in 2019 [14]. RIVM's role is to develop immunological assays for the measurement of antibodies, T-cells and B-cells, and to conduct natural infection and clinical vaccine studies.
The recruitment for the multi-centre BERT study, involving a booster vaccination in four different age groups, has started in October 2017, and the primary outcome (IgG-PT at 28 days) was completed in the Netherlands, the UK and Finland in January 2019. Vaccine antigen-specific IgG and IgA antibody levels in the BERT samples were measured by RIVM. In addition, B-cell responses were determined by measuring circulating antigen-specific plasma cell numbers around day 7 post booster. Furthermore, novel *B. pertussis*-specific T-cell tests are being developed and a whole blood assay is being evaluated as part of the BERT study. Data analysis of measurements is ongoing. The longitudinal samples 1 year after the booster are expected to be completed at the end of 2019.
In addition, preparations for a new infant vaccination study (MINI) are in full progress. The MINI study will focus on innate and adaptive cellular immunity after acellular vaccination in the primary series of infants born from vaccinated and non-vaccinated mothers. The MINI study is expected to start in October 2019.
Lastly, RIVM contributed to the understanding of whooping cough resurgence in Europe by supporting a population genomics project. The RIVM provided WGS data of ~100 strains isolated in the Netherlands between 2010 and2018. Collaborators from France will combine this dataset with sequencing data from approximately 700 *B. pertussis* isolates from all over Europe. This project aims to define the extent and rate of sublineage mixing across Europe, and the interdependence of countries and world regions regarding the impact of their vaccination strategies on *B. pertussis* evolution. The project will also yield insights into the demographic and adaptive dynamics of *B. pertussis* populations across recent times.

7.8.7 Literature

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*RIVM publication

7.9 Pneumococcal disease

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7.9.1 Key points

- In children <5 years of age, introduction of pneumococcal conjugate vaccination (PCV) led to a 59% reduction of IPD in 2018/2019, with only one IPD case caused by any of the serotypes included in 10-valent PCV in 2018/2019. In 2018/19, 71 children <5 years of age with IPD were reported.
- Since 2013/2014, however, the IPD incidence in children <5 years of age has been increasing slightly due to a slow increase of IPD caused by serotypes not included in the 10-valent PCV.
- In other age groups, similar trends were observed with very low incidence of IPD caused by vaccine serotypes and increasing incidence of IPD due to non-vaccine serotypes, compromising the overall impact of PCV implementation.
- Vaccine effectiveness (VE) of at least two doses of PCV10 was 93% (95%CI 80-97%) against vaccine type IPD.
- In 2020, the 23-valent pneumococcal polysaccharide vaccine (PPV23) will be offered to all 60-, 65-, 70- and 75-year-olds in the Netherlands by their general practitioner.

7.9.2 Tables and figures

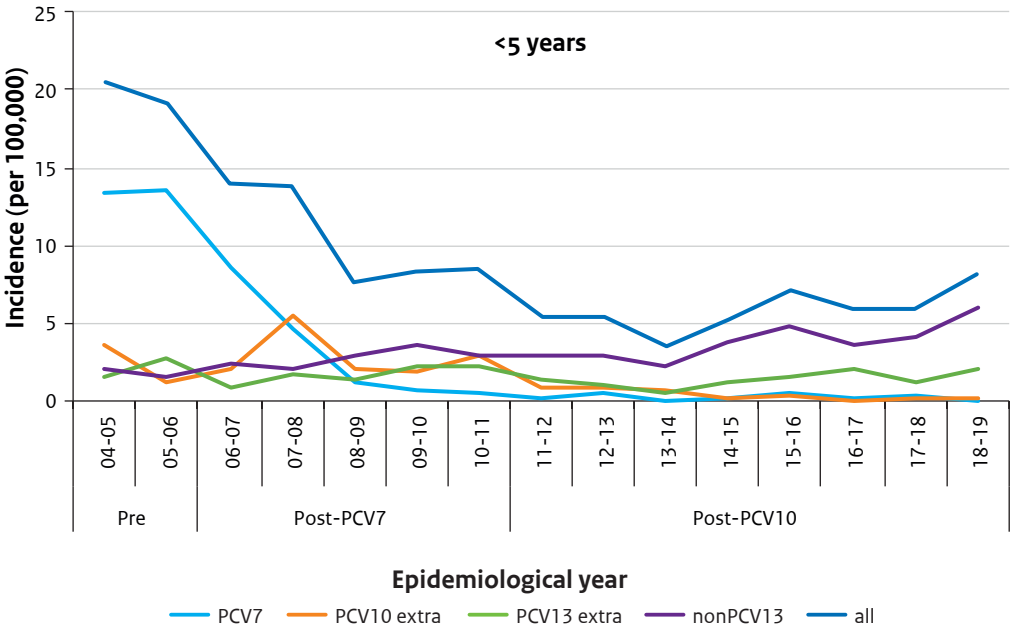

Figure 7.9.1 Incidence of invasive pneumococcal disease (IPD) in children <5 years of age by serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes, non-PCV13 serotypes and all serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)

PCV7 was introduced in June 2006 and PCV10 in May 2011. From 2004-2005 to 2007-2008, sentinel surveillance data have been used and extrapolated to the Dutch population. From 2008-2009 to 2018-2019, data of national surveillance have been used.

Source: NRLBM

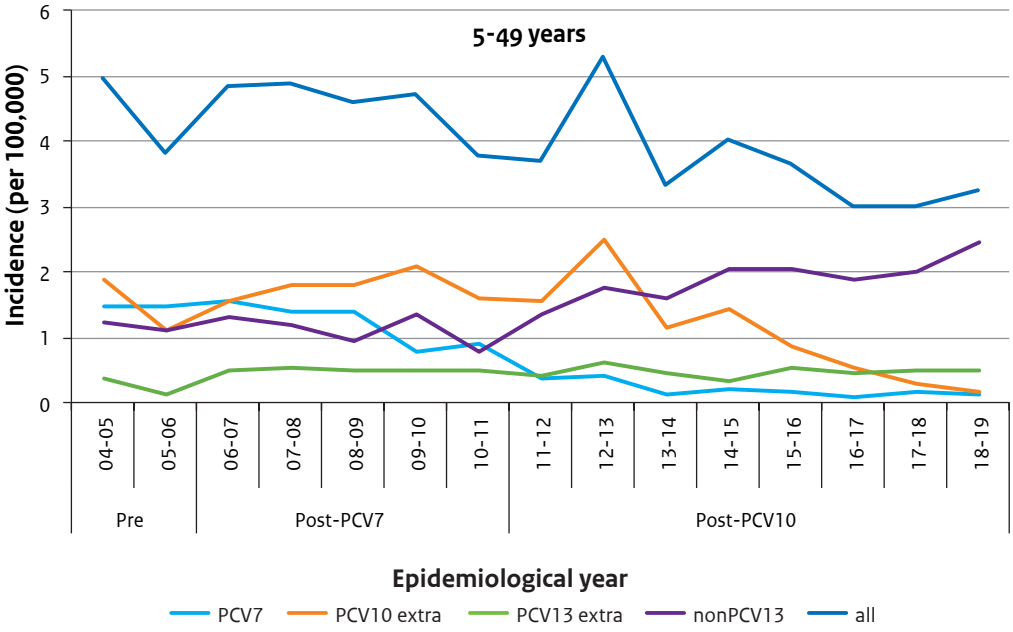

Figure 7.9.2 Incidence of invasive pneumococcal disease (IPD) in persons 5-49 years of age by serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes, non-PCV13 serotypes and all serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)

PCV7 was introduced in June 2006 and PCV10 in May 2011. Sentinel surveillance data have been used and extrapolated to the Dutch population.
Source: NRLBM

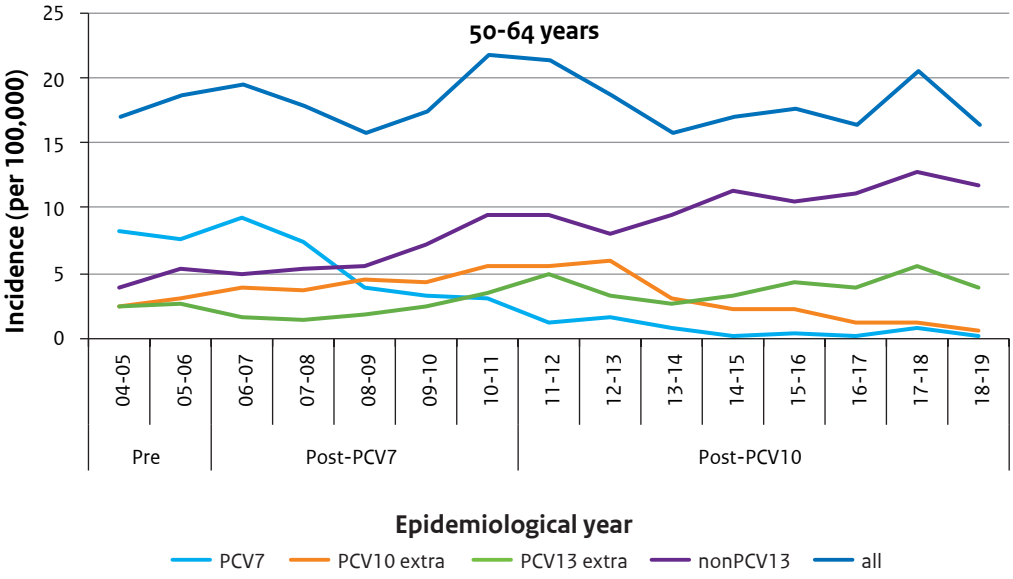

Figure 7.9.3 Incidence of invasive pneumococcal disease (IPD) in persons 50-64 years of age by serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes, non-PCV13 serotypes and all serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)

PCV7 was introduced in June 2006 and PCV10 in May 2011. Sentinel surveillance data have been used and extrapolated to the Dutch population.
Source: NRLBM

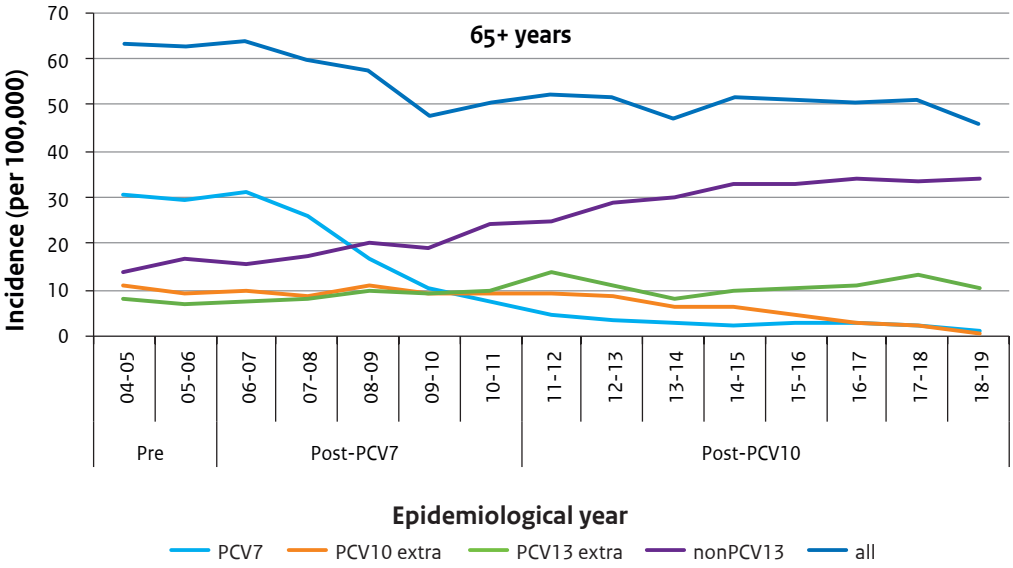

Figure 7.9.4 Incidence of invasive pneumococcal disease (IPD) in persons aged 65 years or more by serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes, non-PCV13 serotypes and all serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)

PCV7 was introduced in June 2006 and PCV10 in May 2011. Sentinel surveillance data have been used and extrapolated to the Dutch population.
Source: NRLBM

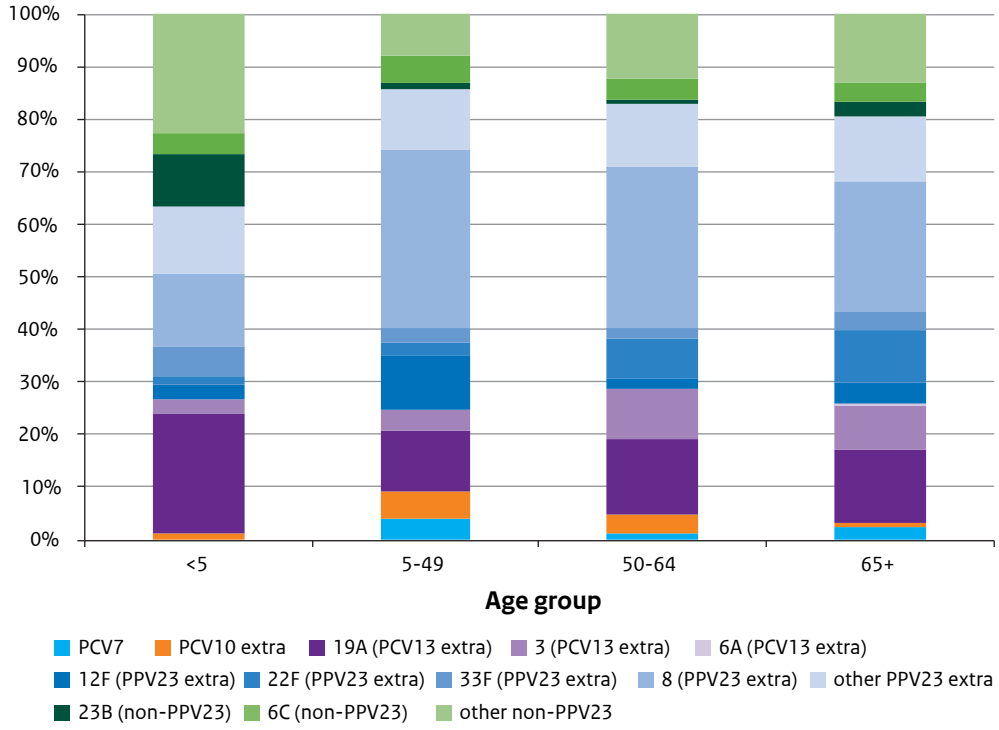

Figure 7.9.5 Distribution of serotypes causing invasive pneumococcal disease (IPD) in epidemiological year 2018/2019

For children <5 years, data of the national surveillance system have been used. For other age groups, sentinel surveillance data have been used.
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	Leukaemia
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 transfusions
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	?
2018	31	1	PCV10	3	?

Source: NRLBM, Praeventis, Osiris

7.9.3 Epidemiology

7.9.3.1 Children <5 years of age (Figure 7.9.1)

In the epidemiological year 2018/2019, 71 IPD cases were reported in children <5 years of age, resulting in an incidence of 8.2 per 100,000. The incidence decreased substantially after the introduction of 7-valent pneumococcal conjugate vaccine (PCV7) in 2006, up to 80% in 2013/2014. However, after 2013/2014 the incidence started rising slightly again. The incidence in

2018/2019 was still significantly lower than before the introduction of PCV7 (59% reduction), but similar to the period just before PCV10 introduction (2011). In 2018/2019, there was only one IPD case caused by any of the serotypes included in PCV10. However, the IPD incidence caused by serotypes not included in PCV10 has been increasing slowly since PCV7 introduction, which explains the increase in overall IPD in the last years. In 2018/2019, there were 18 IPD cases (2.1 per 100,000) caused by the three additional serotypes included in PCV13 but not PCV10 (serotype 3, 6A and 19A, see Table 7.9.1). This incidence has been stable in the last four years. In 2018/2019, the most common serotypes were 19A (16 cases), 8 (10 cases), and 23B (7 cases) (Figure 7.9.5).

7.9.3.2 Persons aged 5-49 years (Figure 7.9.2)

In the epidemiological year 2018/2019, 77 IPD cases were reported by the nine sentinel laboratories (covering 25% of the Dutch population) in persons aged 5-49 years, resulting in an incidence of 3.2 per 100,000. The incidence in this age group has decreased slightly over time since the introduction of PCV7, with a reduction of 26% in 2018/2019. IPD incidence due to serotypes included in PCV10 has decreased substantially since PCV7 introduction, dropping from 3.0 per 100,000 to less than 0.5 per 100,000 in 2018/2019. However, a significant increase has been observed in IPD incidence caused by serotypes not included in PCV10, rising from 1.5 per 100,000 to 2.9 per 100,000 in 2018/2019. In 2018/2019, the most common serotypes were 8 (26 cases), 19A (9 cases), and 12F (8 cases) (Figure 7.9.5).

7.9.3.3 Persons aged 50-64 years (Figure 7.9.3)

In the epidemiological year 2018/2019, 147 IPD cases were reported by the nine sentinel laboratories (covering 25% of the Dutch population) in persons aged 50-64 years, resulting in an incidence of 16.5 per 100,000. The incidence in this age group has been quite stable over time, fluctuating around ~18 per 100,000. IPD incidence due to serotypes included in PCV10 has decreased substantially since PCV7 introduction, from 10.7 per 100,000 to less than 1.0 per 100,000 in 2018/2019. However, a significant increase has been seen in IPD incidence caused by serotypes not included in PCV10, from 7.2 per 100,000 to 15.7 per 100,000 in 2018/2019. In 2018/2019, the most common serotypes were 8 (45 cases), 19A (21 cases), and 3 (14 cases) (Figure 7.9.5).

7.9.3.4 Persons aged 65 years or more (Figure 7.9.4)

In the epidemiological year 2018/2019, 372 IPD cases were reported by the nine sentinel laboratories (covering 25% of the Dutch population) in persons aged 65 years or more, resulting in an incidence of 45.9 per 100,000. The incidence in this age group decreased in the first years after PCV7 introduction and has remained stable over the past 10 years. IPD incidence due to serotypes included in PCV10 has decreased substantially since PCV7 introduction, from 40.2 per 100,000 to less than 1.5 per 100,000 in 2018/2019 (s 96% reduction). However, a significant increase has been seen in IPD incidence caused by serotypes not included in PCV10, from 22.5 per 100,000 to 44.5 per 100,000 in 2018/2019. IPD incidence due to serotypes included in PCV13 but not PCV10 has increased by 41% since PCV7 introduction. IPD due to serotypes not included in PCV13 has increased by 123% since PCV7 introduction. In 2018/2019, 204 (55%) 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 has risen steadily from 10.6 per 100,000 in 2004/2005 to 25.2 per 100,000 in 2017/2018. In 2018/2019, the most common serotypes were 8 (93 cases), 19A (52 cases), and 22F (37 cases) (Figure 7.9.5). In 2020, PPV23 vaccination will be offered to all 60-, 65-, 70- and 75-year-olds in the Netherlands. In 2018/2019, 82% of IPD cases in persons 60 years or older were caused by serotypes included in PPV23.

7.9.3.5 Vaccine failure

Since the introduction of PCV7, 43 cases of vaccine-type IPD have been reported among vaccine-eligible children (born after 1 April 2006 and aged 2 months and over) in the nationwide surveillance. Of these, 20 children (47%) 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, 35%). There was one vaccine failure case in 2018, vaccinated with PCV10.

7.9.3.6 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 2018 that were eligible for PCV10 vaccination and aged 2 months over, and with known serotype and vaccination status.

Eight of the 18 (44%) vaccine type IPD cases were vaccinated with at least two doses, as were 214 of the 233 (92%) non-vaccine type IPD cases. This resulted in a VE of 93% (95%CI 80-97%) for at least two doses of PCV10 compared with zero doses. Serotype-specific VE was 96% (95%CI 74-99%) for serotype 7F. PCV10 was not effective against PCV10-related IPD (type 6A, 6C, 6D, 7A, 7B, 7C, 9A, 9L, 9N, 18A, 18B, 18F, 19A, 19B, 19C, 23A, 23B) with a VE estimate of 11% (95%CI -135 to 66%). Specifically, VE against PCV10-related serotype 19A was 47% (95%CI -49 to 81%). From these results, cross-protection of PCV10 against vaccine-related IPD including serotype 19A cannot be confirmed.

7.9.3.7 IPD mortality

From 2014 to May 2019, 305 IPD cases among children aged under 5 were reported nationally. For 201 cases (66%), the mortality status was known. Fourteen of the 201 (7%) cases died. These 14 cases all had non-vaccine type IPD (serotypes 8 (n=4), 3 (n=2), 22F (n=2), 10A, 12F, 15C, 23A, 24F, 6C). Twelve cases were <2 years of age and four had known comorbidity.

7.9.4 Pathogen

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, 45 potential capsular switches were observed based on MLVA typing. These potential capsular switch events took place in 15

different MLVA complexes (MCs), but some MCs seem more prone to capsular switches than others. Of the 45 isolates, 8 originated from the pre-PCV period, while 13 and 24 isolates, respectively, came from the post-PCV7 and post-PCV10 periods, but the increase of capsular switches over time was non-significant (Fisher exact P=0.14). The three MCs containing the most isolates suspected of capsular switching were MC09V (n=13), MC12F (n=5) and MC14 (n=8) and together these three MCs comprised 56% of the total number of possible switches. The thirteen MC09V isolates switched to four different serotypes (ST) namely ST14 (n=4), ST19F (n=3), ST15A (n=3) and ST24F (n=3). For MC12F the isolates switched to two serotypes, specifically ST07F (n=3) and ST09N (n=2), and all MC14 isolates switched to ST19F (n=8). CgMLST based on 1,210 genes of the 45 isolates showed that all isolates grouped in the minimum spanning tree in the same clusters as with MLVA, thereby confirming the capsular switches. In conclusion, we showed that capsular switches occur within the Dutch invasive pneumococcal population based on MLVA and cgMLST. However, the number and proportion of capsular switches remains very low and increased only slightly over time. Although capsular switches occurred in more than 25% of the MLVA complexes, some MCs seem to be more prone to capsular switching than others.

7.9.5 Current/ongoing research at RIVM

Serological data available from infants vaccinated with PCV10 and PCV13 using the former 2-, 3-, 4- + 11-month schedule in the PIEN and PIM studies were re-analysed in depth to compare the kinetics of serotype-specific antibody levels during the interval between the primary series and the 11-month booster dose [1]. The results indicated that serotype-dependent and vaccine product-dependent antibody patterns could be observed during the interval between the primary series and the booster dose, at the 5-, 8- and 11-month time points. However, levels were not falling under a protective threshold.

A narrative review on pneumococcal vaccination in elderly was conducted [2]. The literature review indicated that several mechanisms related to senescence of the immune system may contribute to increased risk of infectious disease or reduced responsiveness to vaccination. The impact of pneumococcal vaccination at a higher age depends on the epidemiology and the type of (infant) vaccine used as well as on the altering immune system of older vaccinees.

Vaccine-induced serotype-specific antibody immunity cannot cross-protect against all circulating pneumococci. In contrast, antibody and cell-mediated immunity to conserved pneumococcal proteins, acquired through natural carriage and/or infection episodes throughout life, can mediate universal serotype-independent protection. RIVM has started to develop research tools and reagents to learn about the role of protein-specific immunity in samples from various age groups collected in clinical carriage (Okidoki, ILI) and infection (Immfact) studies. One example is the use of various serological techniques to study shifts in protein-specificity of IgG and IgA antibodies. It was shown that susceptibility of older adults cannot be explained by (major) shifts in antibody protein specificity compared with adults and children. Another example of tool development is the successful use of synthetic peptides representing immunodominant protein targets of T-cell immunity, as was recently reported in a proof-of-principle study [3].

7.9.6 (Inter)national developments

7.9.6.1 PCV10 and PCV13

In February 2019, the World Health Organization published their position paper on pneumococcal conjugate vaccines in infants and children under 5 years of age [4]. The paper states that both PCV10 and PCV13 have been shown to be safe and effective and to have both direct and indirect effects against pneumococcal disease caused by vaccine serotypes when used in a 3- or 4-dose schedule. PCV10 and PCV13 have comparable immunogenicity and impact on IPD, pneumonia and nasopharyngeal carriage due to shared vaccine serotypes. While differences were found in their immunogenicity and impact on the three serotypes included in PCV13 and not PCV10 and on serotype 6C, the WHO's position is that there is currently insufficient evidence that the two vaccines differ in their impact on overall pneumococcal disease burden. PCV13 may have an additional benefit in settings where disease attributable to serotype 19A or serotype 6C is significant. The choice of product to be used in a country should be based on programmatic characteristics, vaccine supply, vaccine price, the local and regional prevalence of vaccine serotypes, and antimicrobial resistance patterns.

Hanquet et al report on a multicentre European study estimating the indirect effects of PCV10 and PCV13 vaccination on IPD in older adults across 13 sites in ten European countries [5]. After five PCV10/13 years, the incidence of IPD caused by all types, PCV7 and additional PCV13 serotypes declined by 9% (95% CI: −4% to 19%), 77% (95% CI: 67% to 84%) and 38% (95% CI: 19% to 53%), respectively, while the incidence of non-PCV13 serotypes increased by 63% (95% CI: 39% to 91%). The incidence of serotypes included in PCV13 and not in PCV10 decreased by 37% (95% CI: 22% to 50%) in six PCV13 sites and increased by 50% (95% CI: −8% to 146%) in the four sites using PCV10 (alone or with PCV13). In 2015, PCV13 serotypes represented 20–29% and 32–53% of IPD cases in PCV13 and PCV10 sites, respectively.

7.9.6.2 PCV10

Kilpi et al assessed the VE of PCV10 against pneumonia in the Finnish Invasive Pneumococcal disease (FinIP) vaccine trial, a cluster-randomised double-blind trial including more than 30,000 infants [6]. The VE against all episodes of hospital-diagnosed pneumonia was 27% (95% CI: 14-38). There was no difference in VE between a 2+1 and 3+1 vaccination schedule.

Nieminen et al estimated PCV10 effectiveness in subgroups by sex, gestational age and birth weight in post-hoc analyses of the FinIP vaccine trial [7]. Outcome data included IPD, pneumonia, tympanostomy tube placements, and antimicrobial purchases. Altogether 30,527 infants participated in the FinIP trial, of which 15,503 (50.8%) were boys, 1,519 (5.0%) were born before 37 weeks of gestation, and 1,086 (3.6%) had birth weight <2500 grammes. There were no IPD cases in vaccinated girls, resulting in a VE of 100%, and two IPD cases in vaccinated boys, resulting in a VE of 91% (95% CI: 60-98). The VE was not significantly different between boys and girls; including for other pneumococcal outcomes. There were no IPD cases among vaccinated preterm infants, resulting in a VE of 100%, and two IPD cases among vaccinated term infants, resulting in a VE of 94%. For other outcomes, the VE estimates among preterm infants were also similar to those among term infants.

In Belgium, PCV13 was replaced by PCV10 in Flanders in July 2015, and in Wallonia in May 2016. Desmet et al report on a significant increase in IPD isolates received in 2017 by the National Reference Centre among children 0-2 years compared with 2015 (154 vs 121) [8]. This increase was due mainly to an increase in 19A isolates from 2 in 2015 to 21 in 2017. Before introduction of PCV13, the number of 19A isolates ranged from 56 in 2008 to 83 in 2011.

7.9.6.3 PCV13

Kandasamy et al compared nasopharyngeal pneumococcal carriage in children aged 1-4 years in 2014-2015 (4-5 years after PCV13 implementation) to 2010-2011 (1 year after PCV13 implementation in the UK [9]. Overall pneumococcal carriage was 49% in 2014-2015, of which 96% were non-PCV13 serotypes. Compared with PCV7-immunised children, carriage among PCV13-immunised children was significantly lower for serotypes 19A, 6C and 7F. No significant impact on serotype 3 carriage was found, although a trend towards a reduction was noted. Overall carriage rates were similar between PCV7-immunised children and PCV13-immunised children.

Kent et al estimated the risk of IPD in premature and term infants in England during 2013-2016 [10]. In this period, PCV13 was included in the national immunisation programme in the UK. The incidence was significantly higher in premature infants compared with those born at term (49/100,000 vs 17/100,000; incidence rate ratio 2.87; $p<0.001$) with infants born below 28 weeks gestation having the highest incidence (150/100,000). Most cases were caused by non-PCV13 serotypes (369 cases, 71.4%). The case fatality rate was 6.2%. Premature infants did not have a higher case fatality rate than term infants ($p=0.62$).

Post-licensure studies into PCV13 effectiveness against serotype 3 IPD in children have shown inconsistent results. Sings et al therefore performed a meta-analysis to assess the effectiveness of PCV13 against serotype 3 IPD in children [11]. Four published studies and two conference posters were included. The pooled PCV13 VE was 72% (95% CI: 37-90), supporting direct protection against serotype 3 IPD in children.

7.9.6.4 PPV23

In February 2018, the Health Council of the Netherlands recommended PPV23 vaccination for adults at 60, 65, 70, and 75 years of age. This will be implemented in 2020. GPs will invite eligible persons and will administer the vaccine.

Kim et al studied the effectiveness of PPV23 against IPD and non-bacteraemic pneumococcal pneumonia in adults of 65 years or older in Korea using a hospital-based case-control design [12]. VE against IPD was 28% (95% CI: -6 to 52) and against non-bacteraemic pneumococcal pneumonia 10% (-15 to 31). VE was higher in 65-74 year olds (57% against IPD and 35% against non-bacteraemic pneumococcal pneumonia) compared with patients 75 years or older.

7.9.6.5 IPD

Makwana et al report on a sudden and rapid increase of IPD due to serotype 7C in England and Wales, from 3 cases per year in 2000-2015 to 29 cases in 2016-2017 [13]. The increase was

caused almost entirely by clonal expansion of sequence type 177, which was previously associated with vaccine serotype 19F. Virtually the entire increase occurred in older adults, with no evidence of change in clinical presentation or case fatality rate when compared with other serotypes causing IPD in the same age groups.

7.9.6.6 Cost-effectiveness

7.9.6.6.1 Vaccination of children

The health and economic impact of switching the infant vaccination programme from PCV13 to PCV10 in the context of the Canadian health care system was evaluated [14]. Switching from PCV13 to PCV10 would result in an additional 762,531 cases of pneumococcal disease over 10 years. Although PCV13 has a higher acquisition cost, switching to PCV10 would increase overall costs by over $500 million. PCV13 proved to be cost saving compared with PCV10, even within a 5-year time horizon. This study was funded by Pfizer.

7.9.6.6.2 Vaccination of adults

In Australia, PPV23 was funded for all Australian adults aged over 65 years. A multi-cohort Markov model was developed to retrospectively evaluate the cost-effectiveness of the PPV23 immunisation programme from 2005 to 2015 [15]. The incremental cost-effectiveness ratio (ICER) for PPV23 doses provided from 2005 to 2015 was calculated separately for each year when compared to no vaccination. It was estimated that PPV23 vaccination over the 11-year period prevented 771 hospitalisations and 99 deaths from IPD. However, the estimated IPD cases and deaths prevented by PPV23 declined by more than 50% over this period, likely driven by herd effects from infant PCV programmes. The estimated ICER over the period 2005 to 2015 was approximately AU$224,000/QALY gained compared to no vaccination. When examined per year, the ICER for each individual year worsened from $140,000/QALY in 2005 to $238,000/QALY in 2011 to $286,000/QALY in 2015. The authors conclude that the cost-effectiveness of the PPV23 programme in older Australians was estimated to have dropped over time.

An evaluation was undertaken to assess the cost-effectiveness of sequential use of PCV13 and PPV23, compared with PPV23 alone, in Canadian adults [16]. Two alternative segments of the population were considered: (1) all adults aged 65 years or older, and (2) immunocompromised and high-risk adults aged 65 years or older. For population no. 1, sequential use of PCV13 and PPV23 reduced IPD cases by 1,100, CAP cases by 7,000, and disease costs by $135.8 mln; vaccination costs increased by $254.3 mln, and cost per QALY gained was $35,484. For population no. 2, sequential use of PCV13 and PPV23 reduced IPD cases by 900, community acquired pneumonia (CAP) cases by 6,000, and disease costs by $120.3 mln; vaccination costs increased by $149.8 mln, and cost per QALY gained was $10,728. Funding for this study was provided by Pfizer.

Another study assessed whether a single dose of PCV13 should be reimbursed among Belgian adults aged 65 to 84 years with chronic comorbidities [17]. Use of PCV13 (versus no vaccine) in moderate/high-risk persons aged 65 to 84 years (n = 861,467; 58% vaccination coverage) would be expected to prevent 527 cases of IPD, 1,744 cases of pneumococcal CAP and 176

pneumococcal-related deaths, and reduce medical care costs by €20.1 million. Vaccination costs, however, would increase by €36.9 million and thus total overall costs would increase by €16.8 million. Cost per QALY gained was €17,126. Funding for this study was provided by Pfizer.

Gouveia et al. assessed the cost-effectiveness of PCV13 with no vaccination and PPV23 for Portugal [18]. The ICER of PCV13 versus no vaccination was €17,746 per QALY gained and €13,146 per QALY gained versus vaccination with PPV23. The study was sponsored by Pfizer.

7.9.6.7 Pneumococcal vaccines in development:

Pfizer is developing a 20-valent pneumococcal conjugate vaccine that is being investigated for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* serotypes covered in the vaccine in adults aged 18 years and older. The 20valent-PCV includes the 13 serotypes contained in Prevnar 13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) plus 7 additional serotypes (8, 10A, 11A, 12F, 15BC, 22F and 33F). These 20 serotypes are responsible for the majority of currently circulating pneumococcal disease in adults and six of the seven additional serotypes are associated with high case-fatality rates. Three phase III clinical trials, together enrolling more than 6000 adults, including populations of vaccine-naïve adults and adults with prior pneumococcal vaccination are currently ongoing. Clinical development for use in pediatric populations is in progress.

MSD is developing a 15-valent pneumococcal conjugate vaccine including serotypes 22F and 23F in addition to the serotypes included inPCV13. The vaccine is currently being tested in 11 Phase 3 clinical trials including adults and infants and immunocompromised persons and those at increased risk for invasive pneumococcal disease.
Both vaccines have received a Breakthrough Therapy Designation from the FDA that is designed to expedite the development and review of drugs and vaccines that are intended to treat or prevent serious conditions and preliminary clinical evidence indicates that the drug or vaccine may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).

In addition to PCVs several other vaccine concepts are currently being tested in clinical development programs including (killed) whole cell pneumococcal vaccines (phase I completed) and pneumococcal protein (PnPs) vaccines with proteins that are universally expressed among serotypes (phase I or II). Both vaccine types may induce broader protection while they are also easier to manufacture and less expensive than PCVs.

7.9.7 Literature

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*RIVM publication

7.10 Poliomyelitis

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7.10.1 Key points

- In 2018 and 2019 up to 1 July, no cases of poliomyelitis were reported in the Netherlands, including the Caribbean Netherlands.
- In 2018-2019, polio remained endemic in three countries: Nigeria, Afghanistan and Pakistan.
- No cases of poliomyelitis have occurred in Nigeria since 2016, leaving the entire African region about to being certified wild polio-free in 2020.
- Worldwide, the number of circulating vaccine-derived poliovirus (cVDPV) was less in 2018 (104) compared to 2017 (158) but for the first time in over 10 years all 3 poliovirus types were detected in VDPV outbreaks.
- In addition to several cVDPV2 outbreaks in Africa, from June 2018, two outbreaks of cVDPV1 took place: in Papua New Guinea and Indonesia. A cVDPV3 outbreak was also reported in Somalia, and one cVDPV2 case was reported in China.
- To sustain a world free of all polioviruses, the Global Polio Eradication Initiative (GPEI) released a Polio Endgame Strategy 2019-2023 in 2019.

7.10.2 Tables and figures

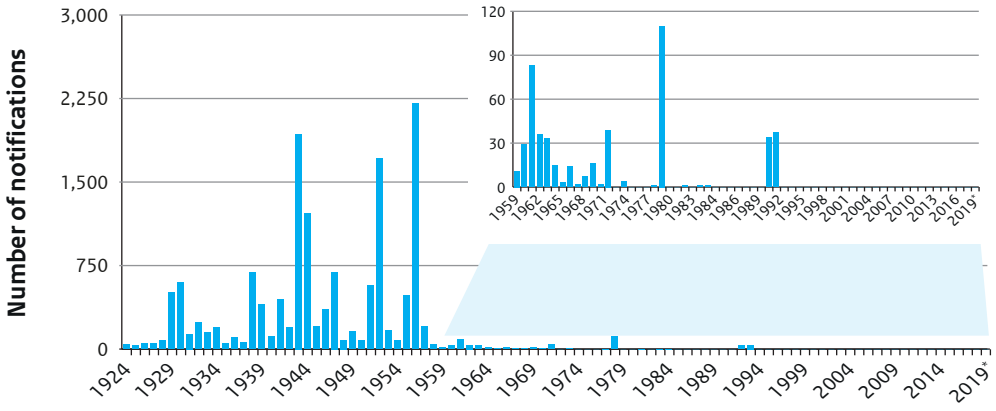

Figure 7.10.1 Notifications of poliomyelitis in the Netherlands from 1924-2019 and zoomed in on 1959-2019* (right part)
*for 2019, reports up to 1 July were included

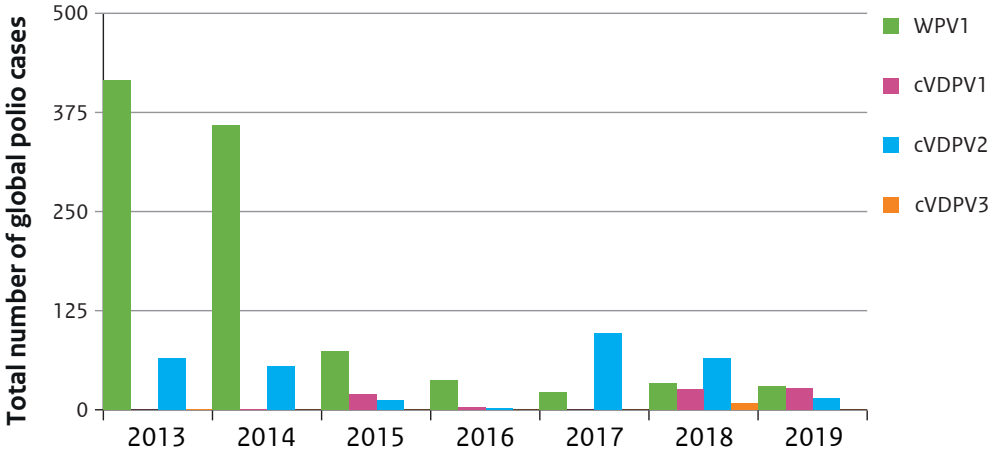

Figure 7.10.2 Total number of global polio cases 2013-2019 as reported to WHO HQ

7.10.3 Epidemiology & pathogen

In 2018 and 2019 up to 1 July, no cases of poliomyelitis were reported in the Netherlands (Figure 7.10.1). Since the accidental cVDPV2 spillage in 2017, no poliovirus has been detected in the Netherlands.

7.10.4 Research

The National Polio Laboratory (NPL) at 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 and samples from immunocompromised children.
Additionally, the NPL developed and piloted an Environmental Surveillance Quality Assurance Programme to support the GPLN and the Environmental Surveillance expansion plan. In cooperation with the immune surveillance department at RIVM, the NPL is developing new serological assays that can be used outside of GAPIII containment. One of the assays is a new anti-PV IgA assay that will be very valuable in the future since it will enable sensitive screening for mucosal contact with infectious polioviruses. After WPV eradication (for all three types), it is anticipated that use of OPV will cease, further increasing the sensitivity of the mucosal contact screening. The essay that is being developed is a Luminex assay using commercially available type-specific anti-poliovirus monoclonal antibodies and IPV. Further optimisation and full test validation is required before the test can be implemented.

7.10.5 International developments

In 2018-2019, polio remained endemic in three countries: Nigeria, Afghanistan and Pakistan. Importation of polio into non-endemic countries was not observed. In 2018 and 2019 up to 1

July, no WPV cases were notified in Nigeria. This means that there have not been any poliomyelitis cases in Nigeria since 2016, putting Nigeria, and the whole WHO African region, about to being declared polio free. Now, the WHO needs to ensure that no WPV cases have been missed and Nigeria has a robust surveillance system in place. In Afghanistan and Pakistan, a combined total of 33 WPV1 cases were notified in 2018, and 42 WPV1 cases in 2019 up to 10 July [2]. In Iran, three WPV1-positive environmental samples have been reported as of 10 July 2019. No public health implications are expected, as Iran has a high vaccination coverage and strong disease surveillance [2].
There were fewer circulating vaccine-derived poliovirus (cVDPV) in 2018 (104) compared to 2017 (158), although the number of outbreaks and the countries affected increased, and for the first time in over 10 years all 3 poliovirus types (cVDPV1, 2, and 3) were detected in VDPV outbreaks (Figure 7.10.2). In 2019 up to 10 July, 22 cVDPV have been reported. Due to the increase in cVDPV2 outbreaks, there has been a higher demand for mOPV2, a WHO-prequalified vaccine with the same operational characteristics as bivalent oral polio vaccine (bOPV). This high demand has even reached the point of threatening stock levels of this vaccine. The WHO advised that all countries should destroy materials containing poliovirus type 2, and provide at least one inactivated polio vaccine (IPV). However, due to the high IPV demand, this has not yet been possible in all countries [3].
In June 2018, Papua New Guinea confirmed a polio outbreak after 18 polio-free years. It concerned a cVDPV1 outbreak. Twenty-six polio cases were identified, with the last case confirmed on 18 October 2018. In addition, seven environmental samples tested positive for poliovirus type 1 [1]. Furthermore, circulation of cVDPV1 unrelated to the outbreak in Papua New Guinea has been confirmed in Indonesia. In total, three genetically-linked isolates were detected from Papua province, one of which from an acute flaccid paralysis case in 2018, and two from healthy community contacts in 2019 [4].
In addition to these two cVDPV1 outbreaks, an outbreak of cVDPV2 and cVDPV3 occurred in Somalia. The outbreak was first detected in environmental sampling in 2017, and continues in 2019. In total, thirteen cases have been identified. All are children below 5 years of age [5]. In China, a cVDPV2 has been confirmed from an acute flaccid paralysis case with onset of paralysis on 25 April 2019. No outbreak has been announced yet as of July 10, as China continues to have a vaccination coverage above 95%.
To sustain a world free of all polioviruses, the Global Polio Eradication Initiative (GPEI) released a Polio Endgame Strategy 2019-2023 in 2019. This so-called roadmap builds on the proven lessons and tools of the strategic plan 2013-2018, and focuses on eradication, integration, containment and certification [3].

7.10.6 Literature

1. *https://www.who.int/papuanewguinea/news/detail/25-03-2019-papua-new-guinea-polio-outbreak-response-report-for-2018-published*
2. *http://polioeradication.org/polio-today/polio-now/this-week/*
3. *http://polioeradication.org/wp-content/uploads/2019/05/polio-endgame-strategy-2019-2023.pdf*
4. *http://polioeradication.org/where-we-work/indonesia/*
5. *https://reliefweb.int/sites/reliefweb.int/files/resources/Somalia%20Weekly%20Polio%20Update_%20Wks%2015-17%202019.pdf*

7.11 Rubella

L. Peckeu, R. Bodewes, W.L.M. Ruijs, N. Rots, R. van Binnendijk, I.K. Veldhuijzen

7.11.1 Key points

- In 2018 and the first six months of 2019, no rubella cases were reported.
- Across Europe, the number of rubella cases continues to decline in 2018.

7.11.2 Tables and figures

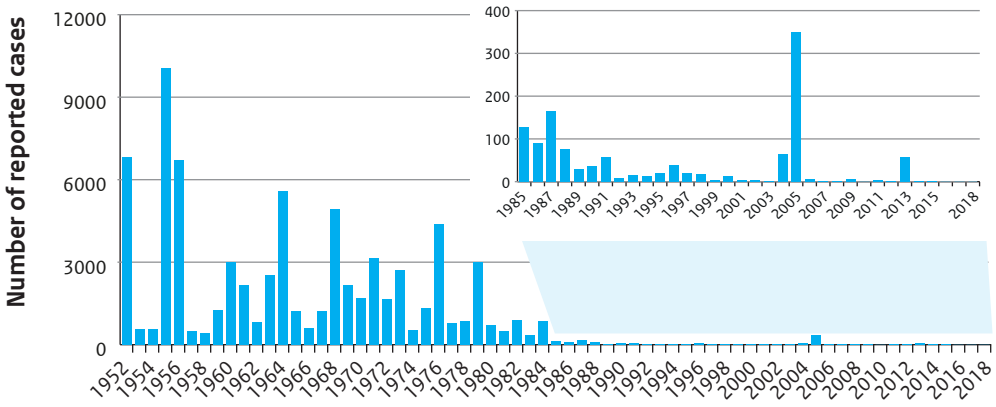

Figure 7.11.1 Annually reported rubella cases since 1952

7.11.3 Epidemiology

In the calendar year 2018 and in the first six months of 2019, no rubella cases were reported. Since 2016 no rubella cases were reported in the Netherlands (Figure 7.11.1).

7.11.4 Research

Infection with rubella virus can cause Fuchs uveitis syndrome (FUS), a chronic eye condition that can lead to cataract and glaucoma [1]. Data from the US showed a decline in the prevalence of FUS since the introduction of rubella vaccination [2]. A recent study described 127 patients seen at the ophthalmology department of Erasmus MC over a six year period who had evidence of rubella virus in ocular fluid [3]. It was observed that the patients with rubella virus-associated uveitis presented with a wider spectrum of clinical manifestations than the typical features of FUS, which were present in 29% of cases. This is relevant as the correct diagnosis of rubella virus-associated uveitis may improve the management of the disease. None of the patients were vaccinated against rubella, and the majority were born before the introduction of rubella-containing vaccine.

7.11.5 International developments

In Europe, reported rubella cases declined from 1,326 in 2016 to 713 in 2017. In 2018, the same tendency was still observed with 579 rubella cases reported by fourteen EU/EEA Member States. Fourteen countries reported no cases. The highest numbers of cases were reported by Poland (450), Germany (58), Italy (23), and Spain (13) [4, 5].

7.11.6 Literature

1. Reef SE, Plotkin SA. Rubella Vaccines. 7th edition ed. Stanley A Plotkin SA, Orenstein WA, Offit PA, Edwards KM, editors. Philadephia: Elsevier; 2018.
2. Birnbaum AD, Tessler HH, Schultz KL, Farber MD, Gao W, Lin P, et al. Epidemiologic relationship between fuchs heterochromic iridocyclitis and the United States rubella vaccination program. Am J Ophthalmol. 2007;144(3):424-8.
3. Groen-Hakan F, van de Laar S, van der Eijk-Baltissen AA, Ten Dam-van Loon N, de Boer J, Rothova A. Clinical Manifestations, Prognosis, and Vaccination Status of Patients With Rubella Virus-Associated Uveitis. Am J Ophthalmol. 2019;202:37-46.
4. World Health Organization. Seventh meeting of the European Regional Verification Commission for Measles and Rubella Elimination (RVC). World Health Organization, 2018.
5. European Centre for Disease Prevention and Control. Monthly Measles and Rubella monitoring report – April 2019. Stockholm: ECDC, 2019.

7.12 Tetanus

Janeri Fröberg, D.W. Notermans, N.A.T. van der Maas

7.12.1 Key points

- In 2018, one case of tetanus was notified. No cases were reported in 2019, up to 1 July.

7.12.2 Tables and figures

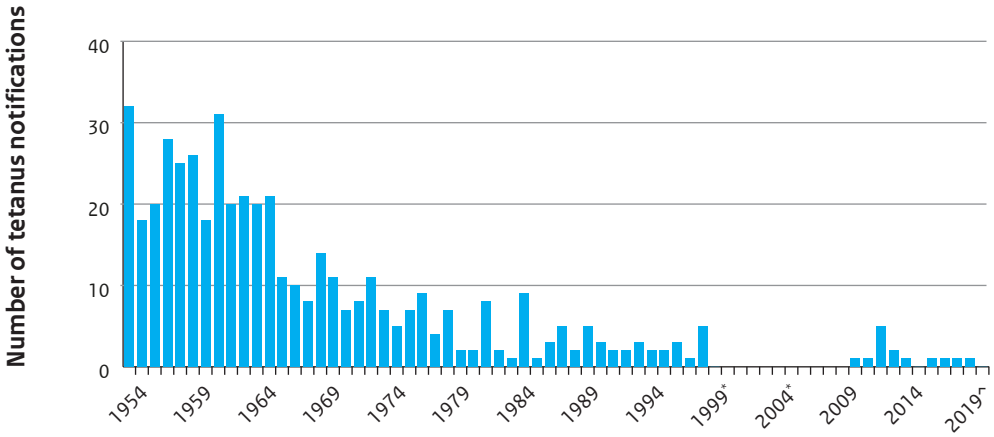

Figure 7.12.1. Reported cases of tetanus in the Netherlands by year, 1954-2019^.
*Between 1999 and 2009, tetanus was not notifiable.
^ For 2019, notifications up to 1 July were counted.

7.12.3 Epidemiology

In 2018, an elderly man was reported with a tetanus infection, based on clinical presentation following the LCI guidelines. It concerned a man whose birth cohort was not be eligible for routine vaccination. According to LCI guidelines, he should have been immunized with Tetanus Toxoid and anti-Tetanus Immunoglobulines. However, he only received Tetanus Toxoid as post-exposure prophylaxis. In 2019 up to 1 July, no tetanus cases were notified.

7.12.4 International developments

As of March 2019, 13 countries worldwide have not yet eliminated maternal and neonatal tetanus, compared to 59 in 2000. The large reduction was mostly due to the Maternal and Neonatal Tetanus Elimination Initiative launched in 1999 [1]. This initiative focuses on improving hygiene during childbirth and vaccinating children. In January 2019, the WHO published a new follow-up guide to sustain maternal and neonatal tetanus elimination and reach true elimination in the remaining countries [2]. The guide explains that antenatal care,

vaccination of pregnant women and clean births are interconnected with the implementation of routine tetanus vaccination, and both are essential to ensure elimination and protection.

7.12.5 References

1. WHO. Maternal and Neonatal Tetanus Elimination (MNTE): WHO; [updated 29 April 2019; cited 2019. Available from: *https://www.who.int/immunization/diseases/MNTE_initiative/en/*].
2. Protecting All Against Tetanus: Guide to sustaining maternal and neonatal tetanus elimination (MNTE) and broadening tetanus protection for all populations. Geneva: World Health Organization; 2019. Licence: CC BY-NCSA 3.0 IGO.

8
Immunisation programme in the Dutch overseas territories, including Dutch Caribbean islands

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8.1 Key points

- In general, vaccination coverage in the Dutch overseas territories, including the Caribbean Netherlands (Bonaire, St. Eustatius and Saba) is high.
- In 2018, no NIP-diseases were reported on Bonaire, Saba and St. Eustatius.
- Data from the Health Study Caribbean Netherlands revealed that protection in the Caribbean Netherlands, overall seroprevalence for measles was relatively high (94%), but lower for mumps and rubella (both 85%).
- Outbreaks of measles and diphtheria, which started in Venezuela due to a humanitarian crisis, remain ongoing in the WHO Region of the Americas. Hence, healthcare workers in the Dutch overseas territories should be alert so as to detect cases and adequately prevent transmission if needed.
- As of 1 January 2019, the age of administration of the booster MMR- vaccine on Bonaire was lowered from 9 years to 18 months in order to ensure timely protection of children.
- Varicella seroprevalence in the Caribbean Netherlands (overall 78%) increases steadily with age; however, unlike in the Netherlands, it increases more slowly and does not reach 100% in the elderly. This results in a population susceptible to varicella at an older age, including pregnant women and elderly, with the potential of developing more severe disease and sequelae.

8.2 Tables and figures

Table 8.1 Vaccination coverage[a,b] in Dutch overseas territories, including Dutch Caribbean islands

	Aruba	Bonaire	Curaçao	Saba	St. Eustatius	St. Maarten
Newborns (2 years)						
No. in cohort 2016	*1,248*	[g] 201	*1,878*	*16*	*34*	*411*
No. of DTaP-IPV-Hib-HBV	1,142	180	1,541	15	28	352
% DTaP-IPV-Hib-HBV	91.5%	89.6%	82.1%	93.8%	82.4%	85.6%
No. of HBV	1,194	n/a	n/a	n/a	n/a	396
% HBV	95.7%	n/a	n/a	n/a	n/a	96.4%
No. of Polio	n/a	n/a	1.532	n/a	n/a	n/a
% Polio	n/a	n/a	81,6%	n/a	n/a	n/a
No. of PCV	1,164	180	1,616	15	28	291
% Pneu	[c] 93.3%	89.6%	86.0%	93.8%	82.4%	70.8%
No. of MMR1	1,190	181	1,678	14	26	370
% MMR1	95.4%	91.4%	89.4%	87.5%	76.5%	90.0%
No. of MMR2	n/a	n/a	1,456	n/a	n/a	n/a
% MMR2	n/a	n/a	[j] 77.5%	n/a	n/a	n/a
No. of Men C	n/a	173	n/a	14	27	n/a
% Men C	n/a	87.4%	n/a	87.5%	79.4%	n/a
Toddlers (5 years)						
No. in cohort 2013	*1,423*	*227*	*	*15*	*46*	*
No. of DTaP-IPV	933	185	*	15	33	*
% DTaP-IPV	[d] 65.6%	81.5%	*	100%	71.7%	*
No. of MMR2	915	n/a	n/a	15	32	*
% MMR2	[d] 64.3%	n/a	n/a	100%	69.6%	*
Schoolchildren (10 years)						
No. in cohort 2008	*1,484*	*251*	*	[k] 22	*33*	*
No. of DTP	664	130	*	[k] 21	32	*
% DTP	[e] 44.7%	[h] 51.8%	*	[k] 95.5%	97.0%	*
No. of MMR2	1,390	153	n/a	[k] 21	n/a	*
% MMR2	[e] 93.7%	[h] 61.0%	n/a	[k] 95.5%	n/a	*

	Aruba	Bonaire	Curaçao	Saba	St. Eustatius	St. Maarten
Adolescent girls (10 years)						
No. in cohort 2008	[f] *773*	*115*	*	[k] *<10*	*17*	*
No. of HPV	[f] 416	32	*	[k] <10	5	*
% HPV	[f] 53.8%	[i] 27.8%	*	[k] 66.7%	29.4%	*

*Unknown because of research-technical issues.

[a] The registration systems in the Caribbean Netherlands are not interfaced with the national population register, so children who have emigrated to neighboring 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 may therefore be higher in reality than shown here. 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] On Aruba, a large proportion is still being caught up in the 2nd year of kindergarten (age 5-6) at school.

[e] On Aruba, DTP-IPV/DT-IPV is given in group 7 (primary school). At the end of 2018, 46.2% of the 2008 cohort was in group 7, of which 88.8% had DTP-IPV/DT-IPV. On Aruba, the age for BMR2 has been brought forward to the age of 4 from cohort 2008, so that the percentage of vaccinees at the age of 10 is more than twice that of DTP-IPV/DT-IPV. Catch-up rounds will follow at school.

[f] On Aruba, HPV is given to girls in group 8 (last year primary school) regardless of age. These figures concern the total school year 2017-2018 instead of the cohort 2008 at the age of 10.

[g] Due to relocation abroad, the number of children in the 2016 cohort for the BMR and MenC vaccination was lower, i.e. 198.

[h] 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 is again invited in June 2018 (girls: HPV2 + DTaP and boys MMR + DTaP). There will also be a campaign devoting extra attention to school vaccinations.

[i] Interim vaccination coverage: in June 2018, these girls were called up for HPV2 (40.9% received HPV1). A number of parents also indicated that they do not want their daughter to be vaccinated until the age of thirteen (just like in the Netherlands).

[j] From 1 May 2017, the BMR2 vaccination will be given at 15 months instead of 4 years. It is possible that not all children have been offered an opportunity to catch up.

[k] On Saba, HPV en MMR/DTaP 9 years old is linked to schoolyear 4th grade. Some of the children are older.

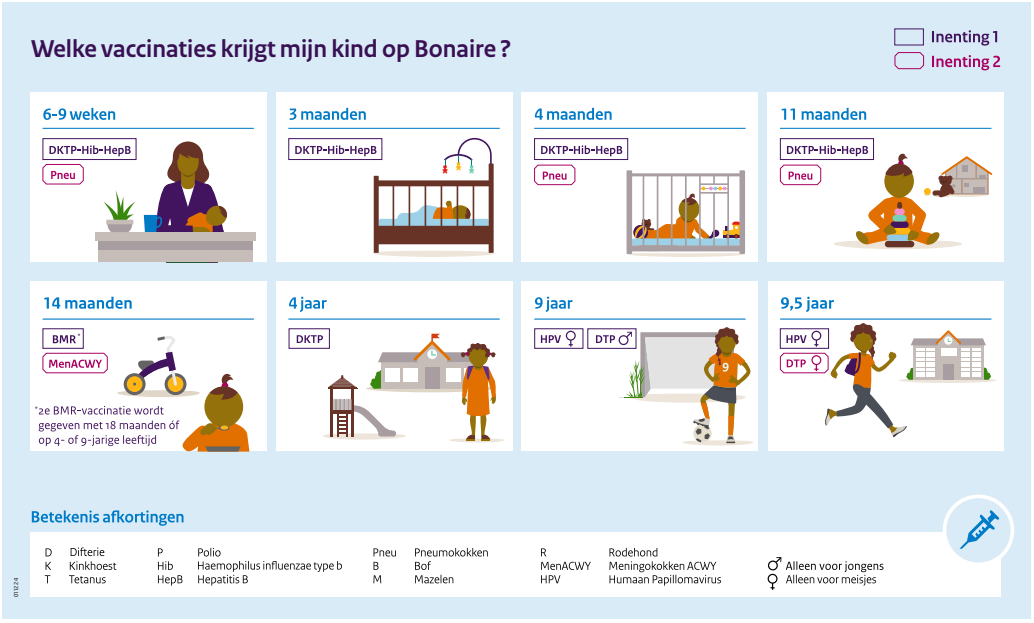

Figure 8.1 Immunisation schedule for Bonaire (in Dutch)

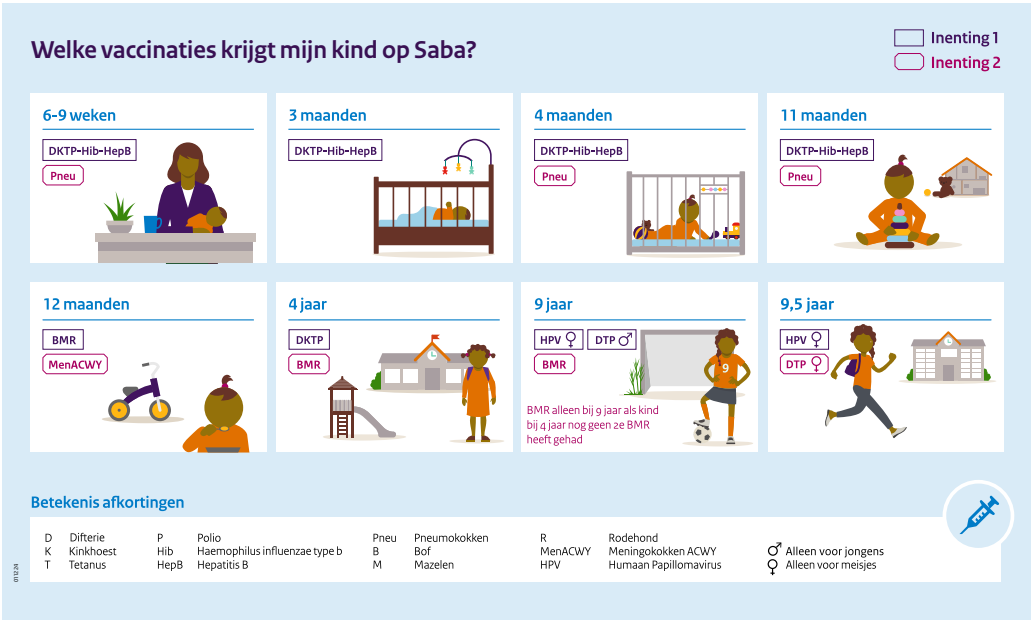

Figure 8.2 Immunisation schedule for Saba (in Dutch)

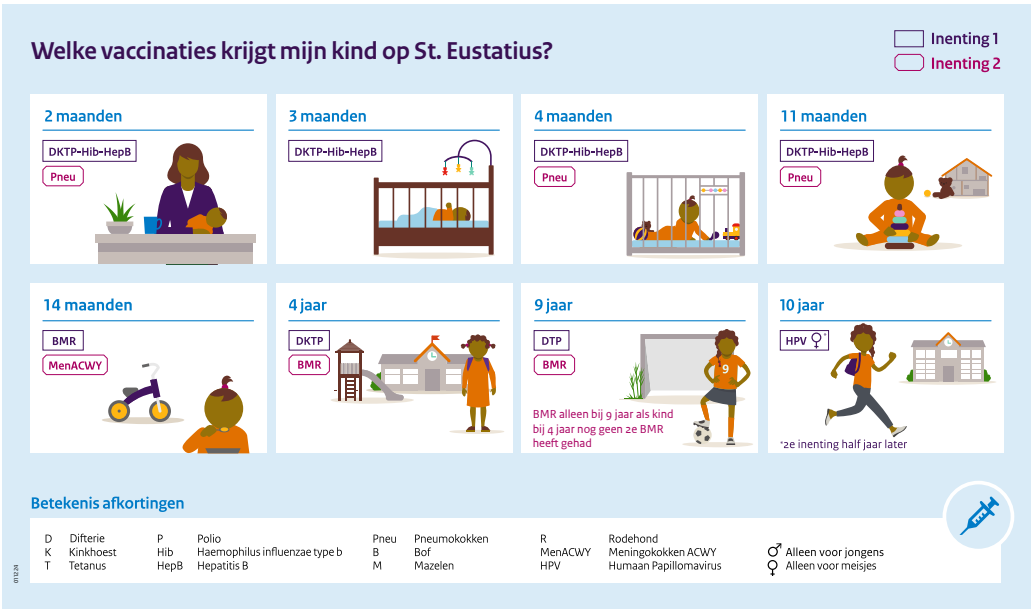

Figure 8.3 Immunisation schedule for St. Eustatius (in Dutch)

Table 8.2 Number of reports of NIP-diseases in the Caribbean Netherlands, 2016-2018

	Bonaire	Saba	St. Eustatius
Diphtheria			
Number of reports in 2016	0		0
Number of reports in 2017	0		0
Number of reports in 2018	0	0	0
***Haemophilus influenzae* type b**			
Number of reports in 2016	0		0
Number of reports in 2017	0		0
Number of reports in 2018	0	0	0
Measles			
Number of reports in 2016	0		0
Number of reports in 2017	0		0
Number of reports in 2018	0	0	0
Meningococcal disease			
Number of reports in 2016	0	0	0
Number of reports in 2017	0	0	0
Number of reports in 2018	0	0	0
Mumps			
Number of reports in 2016	0		0
Number of reports in 2017	0		0
Number of reports in 2018	0	0	0
Pertussis			
Number of reports in 2016	3	0	0
Number of reports in 2017	6	0	0
Number of reports in 2018	0	0	0
Pneumococcal disease			
Number of reports in 2016	0	0	0
Number of reports in 2017	0	0	0
Number of reports in 2018	0	0	0
Poliomyelitis			
Number of reports in 2016	0		0
Number of reports in 2017	0		0
Number of reports in 2018	0	0	0

	Bonaire	Saba	St. Eustatius
Rubella			
Number of reports in 2016	0		0
Number of reports in 2017	0		0
Number of reports in 2018	0	0	0
Tetanus			
Number of reports in 2016	0		0
Number of reports in 2017	0		0
Number of reports in 2018	0	0	0

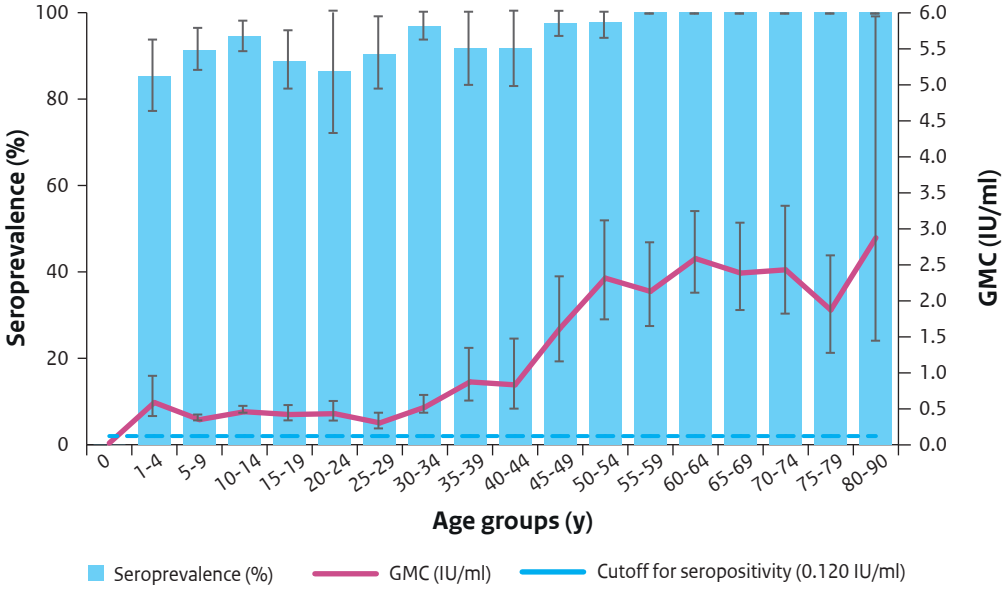

Figure 8.4 Weighted age-specific seroprevalence and geometric mean concentration (GMC) (with 95% confidence intervals) of measles IgG antibodies in the general population of Bonaire, Caribbean Netherlands. Note: antibody concentration ≥ 0.120 international units (IU)/ml is considered protective. Seroprevalence of 95% is considered necessary for herd immunity.

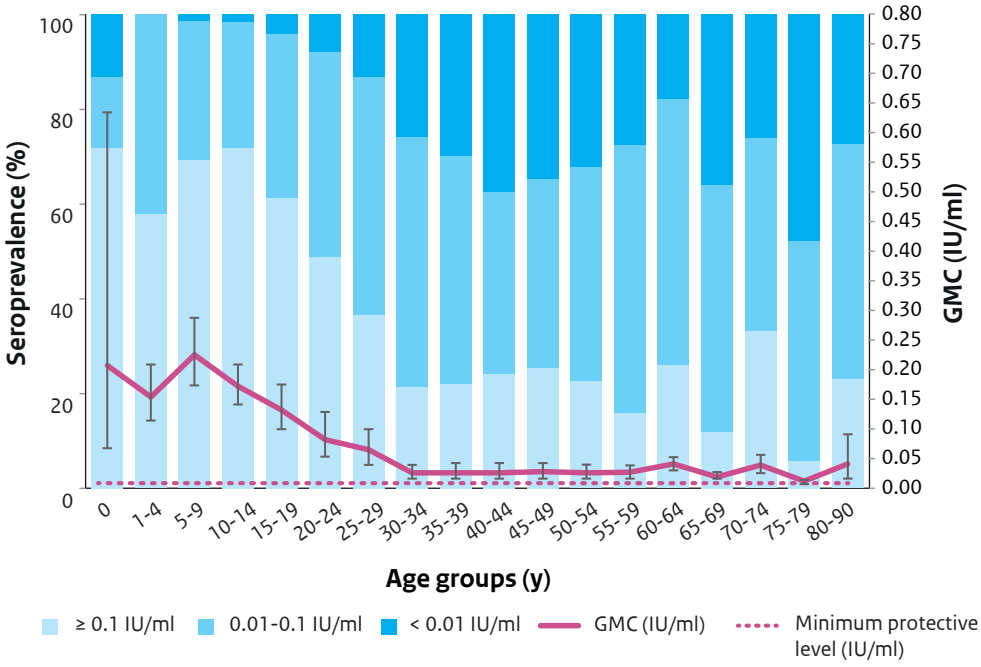

Figure 8.5 Weighted age-specific seroprevalence and geometric mean concentration (GMC) (with 95% confidence intervals) of diphtheria IgG antibodies in the general population of Bonaire, Caribbean Netherlands. Note: antibody concentration < 0.01 international units (IU)/ml is considered non-protective, 0.01-0.1 IU/ml provides basic protection (i.e., 0.01 IU/ml is the minimum protective level), and ≥ 0.1 IU/ml provides full protection. Seroprevalence of 75% is considered necessary for herd immunity in adults.

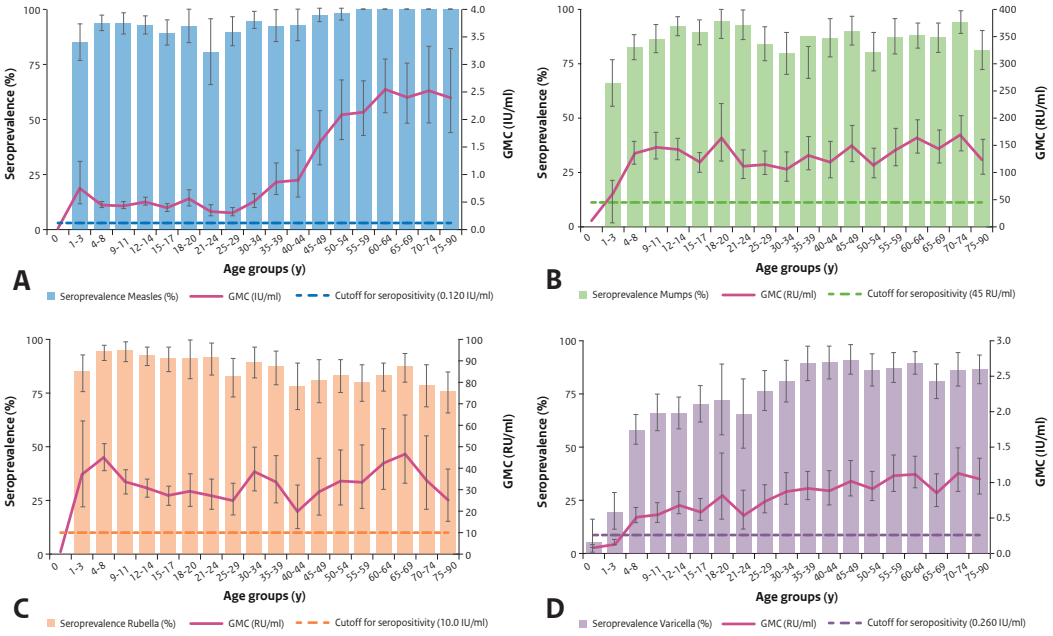

Figure 8.6 Weighted age-specific seroprevalence (%) and geometric mean concentration (GMC) (with 95% confidence intervals) of measles (A), mumps (B), rubella (C), and varicella (D) IgG antibodies in the general population of the Caribbean Netherlands.

8.3 Immunisation schedules

Immunisation schedules in the Caribbean Netherlands (CN) are shown in Figures 8.1-8.3. On Bonaire, from 1 January 2019, the age at which MMR2 is given was brought forward in phases from 9 years to 18 months for all children born on or after 1 January 2018.

8.4 Vaccination coverage

Table 8.1 presents the vaccination coverage in the Dutch overseas territories, including the Dutch Caribbean islands. In general, the vaccination coverage is high. For Curacao and St. Maarten, due to logistical and technical research reasons, not all data on the vaccination rates could be included in this report.

The method for determining the vaccination coverage as used in this chapter often underestimates the number of children in school in this area, since vaccinations are usually offered per school year regardless of the birth year of a child. In that case, the age limits of five and ten years are not always met.

On Saba, an administrative clean-up was performed to establish which children still reside on Saba and what their vaccination status is. Catch-up vaccinations were administered where applicable and possible.

8.5 Epidemiology of diseases included in the NIP

8.5.1 Epidemiology in Bonaire

In October and November 2017, six cases of pertussis were reported by the laboratories. These involved two neonates (3 and 6 weeks old), two children (1 and 12 years old), and two adults. A case study has been done. No epidemiological link was found between these cases. The 1-year-old was not vaccinated. The 12-year-old was fully vaccinated in the Netherlands. Both neonates were not yet vaccinated as they were too young for vaccination at the time.
In 2018, diseases included in the NIP were reported (Table 8.2).

8.5.2 Epidemiology in Saba

No unusual illnesses related to diseases included in the NIP occurred in 2018 (Table 8.2).

8.5.3 Epidemiology in St. Eustatius

No diseases included in the NIP were reported in 2018 (Table 8.2).

8.6 Research

8.6.1 Health Study Caribbean Netherlands

The Health Study Caribbean Netherlands was conducted on Bonaire, St. Eustatius and Saba in May and June 2017. This study has been described thoroughly in [1] – together with the PIENTER study in the Netherlands – and in previous editions of this report. In brief, RIVM partnered with Statistics Netherlands (CBS) and the local Public Health Departments on the islands. This large representative population-based serosurveillance study primarily aimed to investigate immunity against (candidate) NIP-targeted diseases and occurrence of tropical pathogens in the CN. In total, 1,900 people (response rate 25%) were enrolled in the study (*n*=1,829 donated a blood sample and *n*=1,885 filled out a questionnaire), of which 1,197 (26%) on Bonaire, 480 (23%) on St. Eustatius and 223 (22%) on Saba.

8.6.1.1 Risk of measles and diphtheria introduction and transmission on Bonaire

Due to a profound humanitarian crisis in Venezuela, endemic transmission of measles has been re-established as of August 2018. This has resulted in dissemination of the pathogen throughout the World Health Organization Region of the Americas. In addition, outbreaks of diphtheria remain ongoing across Latin America since mid-2016. The crisis has resulted in a large outflow of possibly infected and unvaccinated Venezuelan refugees. As Bonaire is near the coast of Venezuela, the island might be at risk of introduction of these vaccine-preventable diseases. Supported by our serosurveillance study, we measured humoral immunity against measles and diphtheria and discussed the preventive measures for public health accordingly [2].

Figures 8.4 and 8.5 show the weighted age-specific seroprevalence and geometric mean concentration (GMC) for measles and diphtheria, respectively, in the general population of Bonaire. Although overall seroprevalence for measles was high at 93.7% (95% confidence interval (CI) 91.9-95.4), it did not reach the level considered necessary for herd immunity (95%). Certain risk groups could be identified, namely adolescents (12-17 years of age) from Latin America and other non-Western countries and infants below 5 years of age from the Dutch overseas territories & Suriname. Based on these data, the Public Health Department of Bonaire decided to lower the age of administration of the booster MMR vaccine from 9 years to 18 months as of 1 January 2019. For diphtheria, the overall seroprevalence was 78.3% (95% CI 75.2-81.3), and below 75% from 30 years of age onward – a level considered important for herd immunity in adults. In these adults, seropositivity was lowest among female residents from Latin America and other non-Western countries as well as the Dutch overseas territories and Suriname, as these reported to be less vaccinated.

In conclusion, we recommended increased awareness regarding potential introduction of measles and diphtheria on Bonaire, especially in terms of prevention of transmission, taking into account necessary control measures if needed. We also suggested considering (re) vaccination of risk groups as identified and those who are in close contacts with refugees, as well as thorough verification of vaccination status of refugees on arrival if possible, offering vaccination to those eligible. For full details, see [2].

8.6.1.2 Seroprevalence of measles-mumps-rubella (MMR) and varicella in the Caribbean Netherlands

Combined vaccination against measles-mumps-rubella (MMR) has been administered routinely in the CN since the late 1980s (see vaccination schedule above for timing of administration at present). Since the introduction of syndromic surveillance in 2007, no cases of MMR have been detected, however it should be noted that only few potential cases undergo laboratory confirmation. Moreover, similar to the Netherlands, the NIP does not include vaccination against varicella. Nevertheless, relatively large-scale outbreaks throughout the general population of the CN occur every once in a while, the latest of which on Saba affected approximately 250 people (~10% of its population) in 2017 [3]. Data from the present study helped us detect gaps in population immunity against these (candidate) vaccine-preventable diseases.

Overall seroprevalence for MMR in the CN was high for measles (94%), and lower for mumps and rubella (both 85%). All children too young to be vaccinated against MMR in our study (the youngest participants was 3 months of age) were seronegative, i.e., all including infants aged 3-5 months lacked protective maternal antibodies. Seroprevalence for measles in NIP-eligible age groups (i.e., those born in the MMR-vaccination era) was mostly below the threshold for herd immunity (95%) varying between 80-100% (Figure 8.6A). All adults not eligible for vaccination were protected – due to natural infection – and similar risk groups as on Bonaire were identified (see section on measles and diphtheria on Bonaire above). Mumps seroprevalence did not reach 100% in the elderly but remained relatively stable among adults (Figure 8.6B). Seropositivity for rubella was generally high in NIP eligibles, however it was lower among adults who were not eligible for vaccination from the Dutch overseas territories

and Suriname (Figure 8.6C). This finding suggests a specific island epidemiology in the pre-vaccination era differing from that in the Netherlands.

Varicella seroprevalence in CN (overall 78%) increases steadily with age (Figure 8.6D); however, also dissimilar to the Netherlands, far more slowly and does not reach 100% in the elderly. These data underline that a relatively large part of the CN population remains susceptible to varicella at an older age. Contracting varicella at an older age results in more severe disease and sequelae more frequently, especially among the elderly and pregnant women (also affecting the unborn child or even causing miscarriage).

8.7 Literature

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*RIVM publication

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 2018, the number of reported hepatitis A cases (n=188) halved compared to 2017 (n=374), in which we observed a large-scale outbreak among men who have sex with men (MSM).
- The number of cases in 2018 remains higher compared to 2011-2016 (80-125 cases).
- About three-quarters of the patients are 20 years or older.
- Thirty-six per cent of the Dutch cases were reported to be travel-related, with Morocco reported for almost half of these cases.

9.1.2 Tables and figures

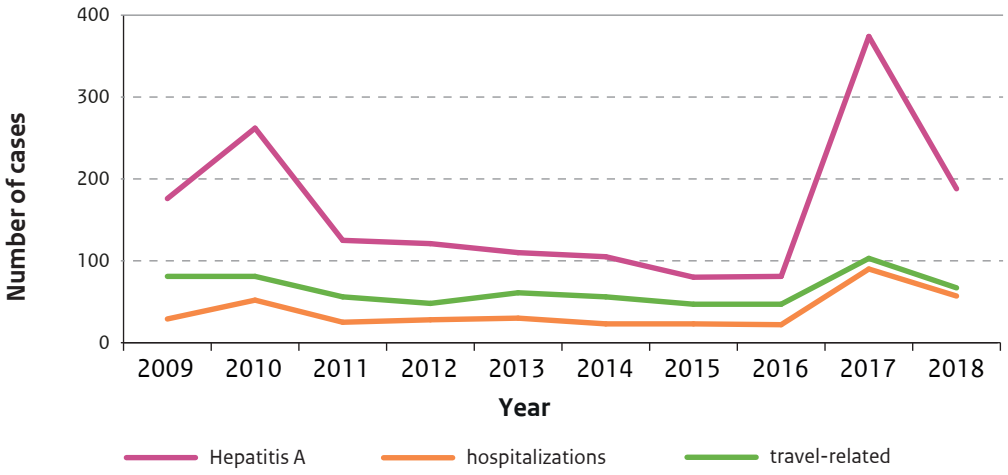

Figure 9.1.1 Number of reported, hospitalised and travel-related cases of hepatitis A, 2009-2018
Source: Osiris

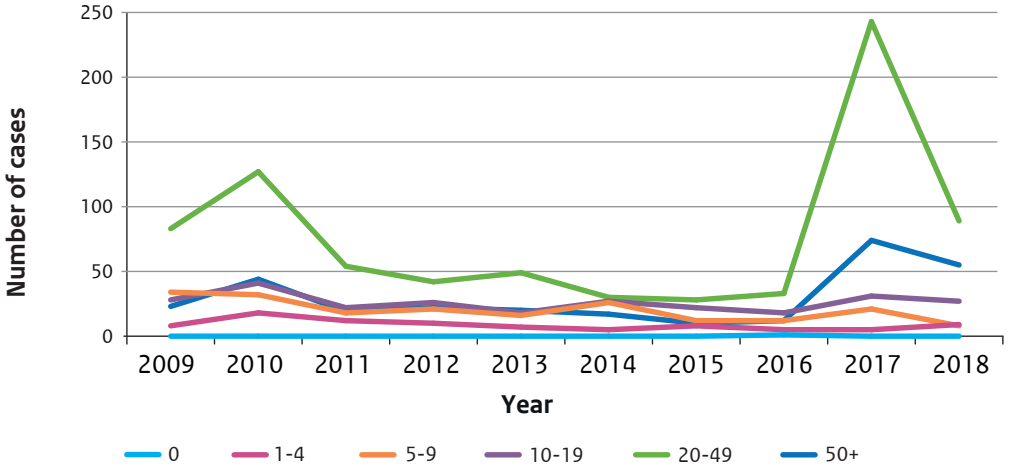

Figure 9.1.2 Age distribution of hepatitis A cases, 2009-2018
Source: Osiris

9.1.3 Epidemiology

A large-scale international hepatitis A outbreak occurred in 2017, with 243 outbreak-related cases in the Netherlands. Two-thirds of these cases were men who have sex with men (MSM) [1]. The outbreak lagged on into 2018, both nationally and internationally [2]. Also, two new strains affecting mainly MSM already caused seven and 29 cases in the first half of 2019.
In 2018, 188 cases of hepatitis A were reported in the Netherlands, of which three on Bonaire, corresponding to 1.1 per 100,000 population. Although this is half of the number of cases in 2017, it is still higher than in the years 2011-2016, in which80-125 cases were reported (Figure 9.1.1 / Appendix 2). No mortality due to hepatitis A was reported in 2018. Infections are mainly seen in 20- to 49-year-olds (Figure 9.3.2). Nevertheless, the proportion of cases in patients aged 50 or over increased, as the number of cases in this age group compared to 2017 decreased much less than in the age group 20-49 years old. Both age groups together account for 77% of the cases. In total 57 patients were hospitalised (30%), which is on the high end of hospitalisation percentages observed in previous years (2009-2017: 16-29%; mean: 22%).

The percentage of travel-related cases ranged between 40% and 59% in previous years (2008-2017), except in 2010 (31%) and 2017 (28%). In 2018, the proportion of travel-related cases was 36% (Figure 9.1.1). Among travel-related cases, Morocco (30/67; 45%) was cited as origin most frequently; other countries were reported five times or less. In several European countries, including the Netherlands, two strains related to travelling to Morocco were circulating in 2018 [3]. Based on the notifications, 17 epidemiologically linked clusters could be deduced, of which 12 clusters were at least partly travel-related (Morocco: five clusters). Five of these epidemiologically linked clusters were molecularly confirmed, with the RIVM-HAV16–090 strain being found in two. In the other clusters, a strain was available for none or only one of the cases within the particular cluster.

9.1.4 Pathogen

Hepatitis A virus (HAV) specific IgM-positive samples can be sent to IDS at RIVM for typing as part of the molecular surveillance of this virus. In 2018, samples were submitted for virus typing of 155 out of 188 reported cases (82%). Samples from the remaining cases were not submitted for various reasons; sometimes because the Municipal Health Service already identified the source. In these cases, it is still worthwhile to sequence a sample because the same strain may show up somewhere else where no clear source is indicated.

Of these samples, 142 (92%) were positive for PCR and could be sequenced. A total of 312 serum and faecal samples from 268 unique persons were tested. HAV RNA was detected in 177 samples (81%) and 139 reported cases, could be typed, which resulted in 51 unique sequences; a total of 100 cases could be assigned to clusters of two or more cases. These concerned 10 molecular clusters varying between two and 44 cases.
The three different strains that circulated in the MSM outbreak in 2017 were still present in 2018: the most common strain was RIVM-HAV16–090 (n=44), followed by VRD_521_2016 (n=22), with the third one (V16_25801) being found 2 times. Two clusters were investigated at the national level because their potential of being foodborne. First, an outbreak was seen among 9 cases with the same strain and 1 case that has an epidemiological link to this molecular cluster. The source of this strain was most likely food. However, a specific food product could not be identified. The second cluster concerned 1 of the 3 MSM outbreak strains (VRD_521_2016), seen in 9 cases in the southwest of the country and without a direct link to MSM. A source could not be found. This cluster could not be distinguished from cases with the VRD_521_2016 strain by sequence analysis of the standard typing fragment of 460 nucleotides. Whole genome sequence analysis of a total of 16 cases of this strain revealed 7 that belong to the cluster that were different in 5 positions from all 9 other whole genome sequences of the same strain. The 7 cases that formed a molecular cluster based on whole genome sequence analysis consisted of 5 cases of the original outbreak cluster, the initially suspected index case with date of onset 3 weeks before the first case in the cluster and an MSM case with date of onset 2.5 weeks before that. Both potential index cases lived in the same region as the cluster. Two other potential index cases have not been sequenced yet. The other molecular clusters were small and/or the infection had been contracted abroad.

9.1.5 Research

A study was done to estimate the risk of hepatitis A among European travellers using surveillance and travel denominator data from 13 European countries [4]. The highest risk was seen in travellers to Africa. Children younger than 15 years accounted for a large proportion (40%) of travel-related cases.

9.1.6 International developments

Travel-related hepatitis A has a large public health impact. The cost-effectiveness of an expansion of publicly-funded hepatitis A vaccination to all travellers to endemic countries was investigated for Ontario, Canada [5]. The current programme for high-risk groups leads to 32.77 QALYs at a cost of $2.10. The expanded programme would provide a mean incremental health gain of 0.000037 QALYs at an incremental cost of $124.31, which means a cost-

effectiveness ratio of $3,391,504 per QALY gained. Based on the analyses, the authors concluded that the expansion of the programme is not considered cost-effective.

The international outbreak among MSM led to 670 confirmed and 93 probable cases of hepatitis A in England between July 2016 and January 2018 [6]. Healthcare costs for these 763 cases were estimated to be around £1,500,000, largely driven by the high proportion (57%) of hospitalisations. One case required a liver transplant due to fulminant hepatitis. In County Durham and Darlington, anti-HAV IgG seroprevalence was measured in HIV-negative MSM attending Sexual Health Services in 2017 [7]. The prevalence of anti-HAV IgG in 171 cases who did not report previous vaccination or infection was 42%. Modelling the costs of pre-vaccination screening and subsequent vaccination of the HIV-negative MSM without anti-HAV IgG versus the costs of universal vaccination of MSM suggests that pre-vaccination screening becomes favourable when anti-HAV IgG seroprevalence exceeds 41%.

Mertoglu et al [8] examined the immunogenicity and safety of inactivated hepatitis A vaccination in children with systemic lupus erythematosus. Thirty patients with systemic lupus erythematosus aged 9-24 years, and 39 healthy subjects aged 6-18 years, were given 2 doses in a 0- and 6-month schedule. All participants were anti-HAV IgM and IgG negative before vaccination. The seroconversion rate one month after the second vaccination was similar for both groups with 80% (patients) compared to 85% (healthy children). Also, no adverse events or increase in systemic lupus erythematosus activity were seen during the study.

A Turkish study investigated the persistence of maternally derived antibodies to hepatitis A [9]. Anti-HAV IgM and IgG were measured in blood samples collected from cord blood of 546 healthy infants and at 12, 18, and 24 months of age. Anti-HAV IgG seropositivity rates decreased from 77.3% at birth to 29.6% (12 months) and 14.8% (18 months), and finally to 17.7% at 24 months of age.

In Brazil, hepatitis A vaccination was included in the vaccination programme as a single-dose schedule in 2014 [10, 11]. The humoral response after vaccination was assessed in a cross-sectional study with 252 vaccinated children [10]. A total of 93.6% of these children were anti-HAV positive, at a mean time of 262 days after vaccination. The impact of this vaccination strategy was evaluated by analysing the incidence of hepatitis A over the years 2010-2017 [11]. Incidence of hepatitis A was between 3.02 and 3.48 per 100,000 in the period 2010-2014 and dropped to 1.46 (2015), 0.47 (2016), and 0.72 (2017) per 100,000. The decrease was independent of gender and geographical macroregions, but most significant in the group aged under 5 years, which was the target population for vaccination. The slight increase in incidence in 2017 was caused by a significant outbreak among young adult males, mainly in the city of Sao Paulo. The decrease in incidence in females and children continued in 2017.
China introduced vaccination against hepatitis A in 1994, which was free of charge to parents after integration in the National Expanded Programme on Immunisation in 2008 [12]. Vaccination is given at the age of 18 and 24 months. The coverage rate of both doses is above 99%. In 2011, a catch-up programme among children born after 2002 was carried out. Anti-HAV IgG prevalence in the population was 68.2%, 81.7% and 82.5% in respectively 1992, 2006

and 2014. The incidence of reported hepatitis cases in 1999 was 59.41 per 100,000, which declined to 0.80 per 100,000 in 2017. The largest decrease was seen in the (vaccinated) age group 0-10 years.

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*RIVM publication

9.2 Respiratory Syncytial Virus

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

9.2.1 Key points

- A total of 106 RS viruses (12%) were detected in 863 combined nose and throat swabs of ILI and other ARI patients, collected by sentinel GPs in the 2018/2019 respiratory season, compared to 6% in 2017/2018 and 12% in 2016/2017.
- The primary endpoint of a phase 3 maternal RSV vaccine, i.e. prevention of medically significant lower respiratory tract infections due to RSV, was not met (VE 39%; 95%CI -1%- +64%). The FDA strongly recommended performing a second efficacy trial.
- In a phase 2b trial, a long half-life anti-RSV monoclonal MEDI8897 showed 70.1% (95%CI 52.3%-81.2%) relative risk reduction of medically attended lower respiratory tract infections due to RSV and 78.4% (95%CI 51.9%-90.3%) reduction of RSV hospitalisations.

9.2.2 Tables and figures

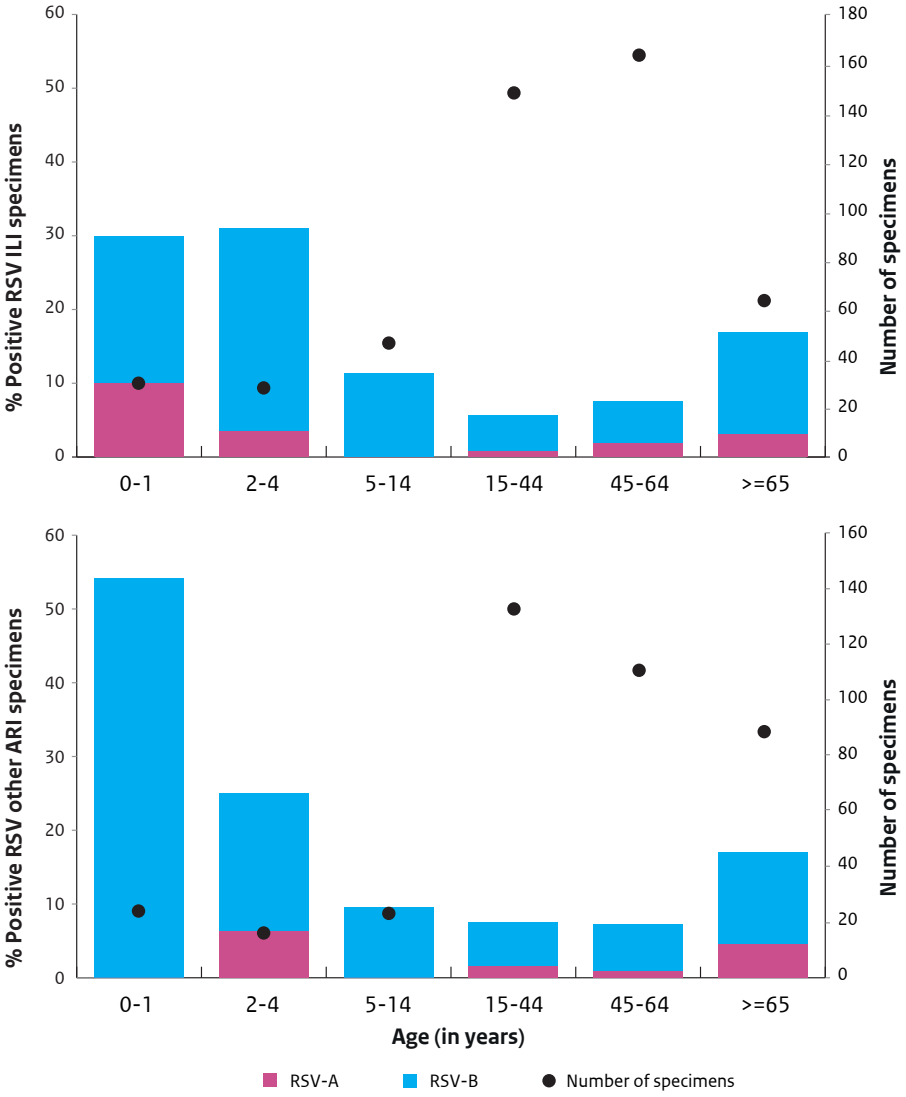

Figure 9.2.1 Percentage of RSV-A and RSV-B positive specimens from patients with influenza-like illness (ILI, panel A) and other acute respiratory infections (ARI, panel B), and the number of tested specimens, taken by sentinel general practitioners (GPs) from community patients during the respiratory season of 2017/2018 (week 40 of 2018 - week 20 of 2019), displayed for six age groups.

Source: NIVEL Primary Care Database, RIVM

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

9.2.3 Epidemiology and pathogen

Studies show that RSV is a common cause of respiratory infections in young children [1, 2] and in the elderly [3, 4], causing outbreaks in elderly care facilities [5]. RSV is subdivided in RSV-A and RSV-B based mainly on the variation in the attachment protein, the G-protein.

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

In the 2018/2019 season, 106 RS viruses were detected in 104 out of 863 nose and throat swabs (12.1%) collected from patients with ILI or other ARI by sentinel GPs (two patients had a double infection with RSV-A and RSV-B). The percentage of positive specimens from the GP sentinel surveillance was higher in this season compared to the 2017/2018 (6.1%) season and comparable to the 2016/2017 season (12.0%).
Furthermore, the weekly reporting of virological laboratory surveillance by 20 virology laboratories yields insights into the number of positive RSV tests, reflecting RSV circulation. These data can be used to define the RSV epidemic season and epidemic intensity [6, 7]. These specimens are collected mainly from children [7].

Of the 106 virus specimens from the virological laboratory surveillance, 18 were RSV-A (17%) and 88 were RSV-B (83%). Two patients had a double infection with RSV-A and RSV-B.
The percentage of positive samples was highest in the 0-1 year age range (30% in ILI cases and 54% in other ARI cases) (Figure 9.2.1).
For more information on epidemiology in the Netherlands, please refer to the annual report 'Surveillance of influenza and other respiratory infections in the Netherlands: winter 2018/2019' [7].

9.2.4 Research

European collaboration on surveillance of RSV and better harmonisation in both epidemiological and virological aspects of surveillance are important to strengthen RSV surveillance at the national and European levels. RIVM plays an important part in European initiatives relating to RSV surveillance and collaborates closely with ECDC and other public health institutes, specifically SSI (Denmark).
Also, RIVM is a partner in the RESCEU project ([http://resc-eu.org/], which is funded by the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement 116019. This project aims to explore the clinical, economic and social burden caused by RSV and strengthen European-wide collaboration on the part of the many different disciplines working on RSV.

Additionally, a thorough understanding of the immunological mechanisms underlying (vaccine-induced) protection against RSV is essential for advising on the implementation of novel vaccines.
Previous research has indicated that antibody titres and virus neutralisation are poor predictors of RSV protection, suggesting that other antibody functions might be important [8].

In the past year, we published a review article summarising what is known on antibody functionalities beyond neutralisation in the context of RSV infection. We found that the existing literature provides numerous indications that Fc-mediated effector functions might contribute to protection and have therefore urged the field to take these functions into account in the design and evaluation of novel vaccines [9]. In addition, we have shown that certain immune cells (natural killer cells) can be infected by RSV, which has a profound effect on their in vitro functionality [10]. Since infection of these cells can be increased in the presence of virus-specific antibodies, this finding is important for our understanding of the potential effect of (maternal) RSV vaccination on protection and disease.

9.2.5 International developments

Recently, results of a phase 3 clinical trial of a maternal RSV vaccine were published [11]. The primary endpoint of a phase 3 maternal RSV vaccine, i.e. prevention of medically significant lower respiratory tract infections due to RSV, was not met (VE 39%; 95%CI -1%- +64%). However, the effectiveness against infant RSV hospitalisations was estimated at 44.4% (95%CI 19.6-61.5%) and against RSV disease with severe hypoxemia 48.3% (95%CI -8.2 - +75.3). There were large differences between the participating study sites, with low effectiveness being associated with late gestational age immunisation and short intervals to birth. The FDA strongly recommended that a new efficacy trial be undertaken before registration. The same vaccine was tested in the elderly but failed to show a level of protection [12].
A phase 2b randomised control trial in 29- to 35-week healthy preterm infants <8 months of age showed that up to 150 days post administration, the monoclonal antibody provided a 70.1% (95%CI 52.3%-81.2%) relative risk reduction of medically attended lower respiratory tract infections due to RSV. Likewise, the study showed 78.4% (95%CI 51.9%-90.3%) reduction of RSV hospitalisations.
Several other RSV vaccines and monoclonals are in different stages of development [*https://vaccineresources.org/files/RSV-snapshot-2019_04_05_April_High%20Resolution.pdf*].

9.2.6 Literature

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*RIVM publication

9.3 Rotavirus

P. de Oliveira Bressane Lima, J.D.M. Verberk, A.W.M. Suijkerbuijk, R. Pijnacker, I.K. Veldhuijzen, M. Mollers, J.A.P. van Dongen, H. Vennema, M. Hooiveld, P. Bruijning-Verhagen, H.E. de Melker.

9.3.1 Key points

- The rotavirus season in 2018 was comparable to that in 2017, contradicting the previous hypothesis of a biennial pattern that was formulated due to low-endemic rotavirus seasons in 2014 and 2016. Until mid-July 2019, fewer rotavirus cases have been observed compared to the same period in 2018.
- In July 2018, the Ministry of Health, Welfare and Sport decided to offer vaccination to infants belonging to risk groups. The process of implementation is ongoing.
- G9P8 and G3P8 were the most prevalent genotypes in 2018.
- A thermostable vaccine (ROTASIIL) has achieved WHO prequalification. Four rotavirus vaccines are currently available worldwide, of which two (Rotarix and RotaTeq) are licensed for use in Europe.

9.3.2 Tables and figures

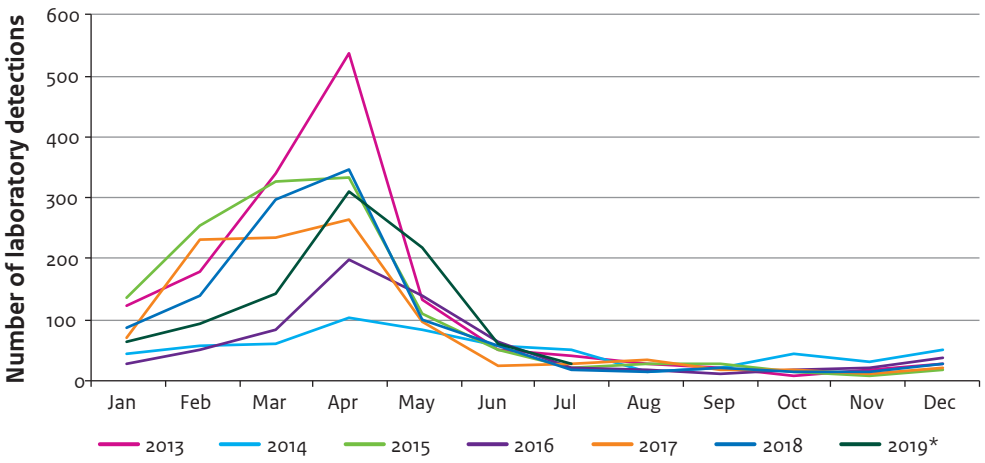

Figure 9.3.1 Number of reported laboratory rotavirus detections per month in the Netherlands, 2013-2019* (*up to mid-July)

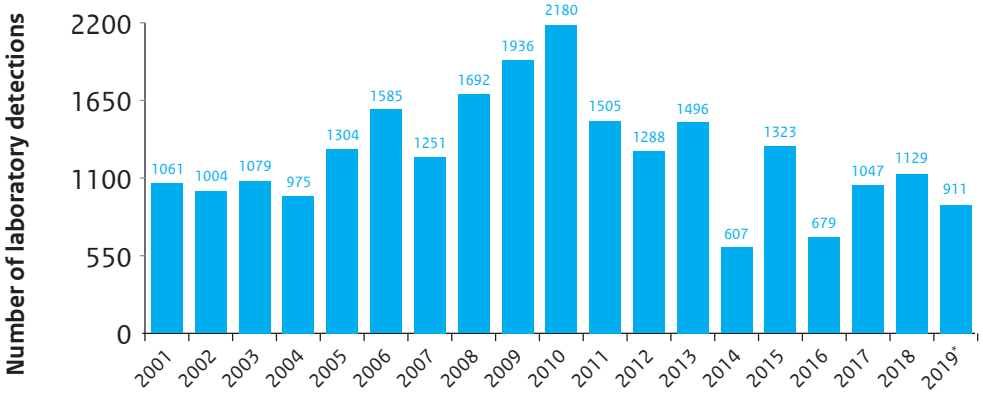

Figure 9.3.2 Number of reported laboratory rotavirus detections per year in the Netherlands, 2001-2019* (*up to mid-July)

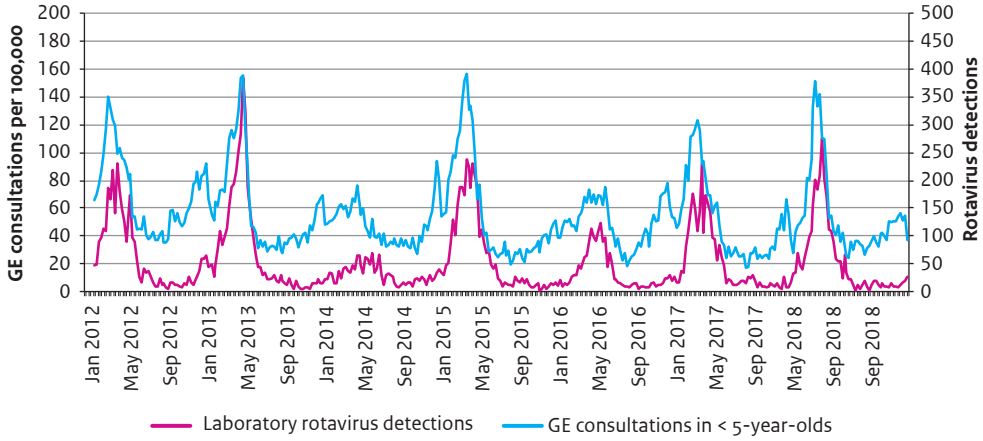

Figure 9.3.3 Overall number of rotavirus laboratory detections and general practice all-cause gastroenteritis consultation in children under 5 years of age, the Netherlands, 2013-2018

Table 9.3.1 Number of rotavirus samples typed per year and identified genotypes, the Netherlands, 2013-2018

Type	2013	2014	2015	2016	2017	2018	Total
G12P8	1	6	2	0	1	2	12
G1P8	**83**	20	25	9	23	7	167
G2P4	41	29	34	12	12	6	134
G3P8	51	7	14	23	**38**	56	189
G4P8	35	12	**137**	3	23	3	213
G9P8	23	**49**	32	**59**	20	**60**	243
G9P4	1	0	1	0	8	29	39
Other	52	16	27	12	42	16	165
Total	287	139	272	118	167	179	1,162

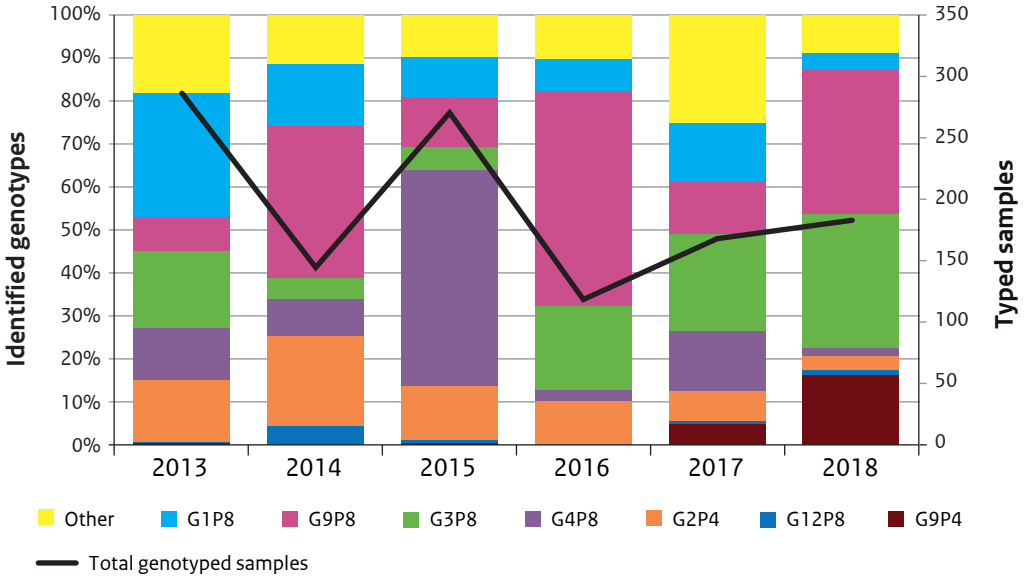

Figure 9.3.4 Absolute number of rotavirus samples genotyped per year and identified genotypes rate, the Netherlands, 2013-2018

9.3.3 Epidemiology

9.3.3.1 *Weekly virology report*

In 2018, most rotavirus laboratory detections were reported between February and May (more than 30 rotavirus laboratory detections per week), with a peak in the first week of April (110 rotavirus laboratory detections) (Figure 9.3.1). In 2018, 1,129 rotavirus cases were notified, slightly more than in 2017 (n=1,047). The rotavirus cases detected in 2018 still account for fewer detected cases per year than those notified between 2005 and 2013 (range: 1,251-2,180 detections per year). Data from 2019 up to mid-July show slightly fewer rotavirus cases compared to the same period in 2018 (2018 n=1,033; 2019 n=911).

Until 2013, the rotavirus seasonal pattern in the Netherlands was consistently annual, with yearly detections varying around 1,000 to 2,200. The remarkably low seasons in 2014 (n=607 detections) and 2016 (n=679 detections) led to the hypothesis of a shift in the rotavirus seasonal pattern to a biennial pattern. However, the rotavirus seasons in 2017, 2018 and up to mid-July 2019 contradict this hypothesis (Figure 9.3.2) [1].

9.3.3.2 *NIVEL*

The NIVEL Primary Care Database provides data on all-cause gastroenteritis (GE) in children under the age of 5 consulting the general practitioner [2].

In 2018, 7,065 all-cause GE consultations were reported per 100,000 children younger than five years of age (on average 138 per 100,000 per week); slightly more consultations than in 2016 (n=6,380 per 100,000) and 2017 (n=6,536 per 100,000). The consultations occurred more frequently between January and May with a mid-March peak (378 per 100,000 children per week). Only in this period of the year, 4,160 consultations per 100,000 children were registered; which is quite similar to the number of consultations registered in the same period in 2017 (n=4,176 per 100,000).

The number of all-cause GE consultations between January and May seems to be affected by the rotavirus season pattern (Figure 9.3.3). In 2014 and 2016 – when the rotavirus season was exceptionally low – remarkably fewer consultations per 100,000 children were registered (2014: n=3,033; 2016: n=3,191) compared to the same period in 2012 (n=4,785), 2013 (n=4,680), and 2015 (n=4,906).

9.3.4 Pathogen

In 2018, 87% of the received samples (n=179/206) could be typed. Half of the typed samples (89/179) were identified as rotavirus G9, which comprises the genotypes G9P8 and G9P4. The most frequently detected genotypes in 2018 were G9P8 and G3P8 accounting for 34% (60/179) and 31% (56/179) of the typed samples, respectively. The increase in detections of genotype G9P4 in the last two years (2017: n=8; 2018: n=29) was remarkable, since this genotype was hardly found prior to 2017.

9.3.5 Research

9.3.5.1 *RIVAR study*

From May 2016 until December 2019, the RIVAR study (Risk-Group Infant Vaccination Against Rotavirus) offers rotavirus vaccination to high-risk infants (i.e. infants with severe congenital pathology, prematurity and/or low birth weight) born in one of the thirteen Dutch hospitals participating in this study. This project is a pilot study on the feasibility and effectiveness of rotavirus vaccination in high-risk infants. Of the infants eligible for rotavirus vaccination identified during the RIVAR study, 60% were vaccinated on average. The vaccination rate ranged from 34% to 81% among the participating hospitals and was higher in general hospitals (range 48-82%) compared to academic hospitals (range 34-51%). It is hypothesised that the lower vaccination rate in academic hospitals might be the result of i) the transfer of eligible infants to non-participating hospitals, ii) fear of the theoretical risk of spreading the vaccine virus strain in clinical wards, iii) infants who are still critically ill beyond 14 weeks of age might not be vaccinated and iv) the availability of the rotavirus vaccine might not be routinely discussed with parents [3]. Among 291 vaccinated infants with gestational age <30 weeks, two serious adverse events were identified (i.e. need for respiratory support after the concomitant administration with NIP vaccines and sepsis of unknown pathogen. The relation of these events with the vaccine could not be excluded, although other causes might also be possible.

9.3.6 Cost-effectiveness

A study re-evaluated the cost-effectiveness of rotavirus vaccination in the Netherlands, taking into account the recent changes in rotavirus epidemiology, which includes the low endemic years observed in 2014 and 2016. The results showed that targeted rotavirus vaccination of infants with heightened-risk medical conditions (i.e. prematurity, low birth weight or severe congenital pathology) is a cost-saving strategy, but further reductions in the vaccine price would be necessary for universal rotavirus vaccination to become cost-saving [5]. A more recent study assessed the cost-effectiveness of a universal routine infant RV vaccination programme and its budget impact on the Regional Health Service of Piedmont, Italy, in order to evaluate the opportunity of the implementation of a national rotavirus vaccination programme. In this study the costs and benefits of a Rotarix two-dose vaccination were compared with a non-vaccination strategy. The intervention proved to be cost-saving. Vaccination costs included in the model were rather low: €33.50 per dose based on the Piedmont Region tender price (instead of the market price mostly used in economic evaluations) [6].

9.3.7 (Inter)national developments

In July 2018, the Ministry of Health, Welfare and Sport decided to offer vaccination to infants belonging to risk groups. The process of implementation is ongoing.
Up to August 2018, 98 countries worldwide introduced rotavirus vaccination in their national immunisation programmes. Among the ten countries with the highest numbers of rotavirus-related deaths, only six have introduced rotavirus vaccination (Afghanistan, Angola, Ethiopia, India, Kenya, and Pakistan) [8].

In 2018, the thermostable rotavirus vaccine ROTASIIL (human-bovine reassortant rotaviruses G1, G2, G3, G4, G9) achieved WHO prequalification. This vaccine may have a major impact on the cost and availability of rotavirus vaccination, since it is the first rotavirus vaccine which does not require constant refrigeration [9, 10]. ROTASIIL is the fourth WHO prequalified rotavirus vaccine besides Rotavac (attenuated human rotavirus strain G9P[11]), Rotarix (attenuated human rotavirus strain G1P[8]), and RotaTeq (human-bovine reassortant rotaviruses G1, G2, G3 G4, P[8]). Only Rotarix and RotaTeq are licensed for use in Europe [11].

A study in the USA on rotavirus vaccination effectiveness in the period 2001-2016 analysed national data on hospitalisation due to rotavirus GE or all-cause GE and data on children vaccination status. The rotavirus vaccine effectiveness was estimated at 87% in preventing rotavirus GE hospitalisation among 0- to 4-year-old children. The infant rotavirus vaccination was also observed to have an important indirect effect across all age groups [12]. A systematic literature review on the effectiveness and impact of rotavirus vaccination in Europe between 2006 and 2014 shows a significant health benefit of the rotavirus vaccine, with vaccine effectiveness against rotavirus GE hospitalisations ranging between 80% to 98% and a reduction in rotavirus-related hospitalisations by 65% to 84% [13].

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*RIVM publication

9.4 Varicella zoster virus (VZV) infection

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9.4.1 Key points

- The VZV epidemiology (incidence of GP consultations, hospitalisations and deaths) in the Netherlands has not changed in recent years and is comparable to that in previous years; in 2017 GPs recorded about 48,000 varicella and 90,000 herpes zoster episodes (280 and 530 episodes per 100,000 population respectively).
- In 2019, the Health Council of the Netherlands issued a positive recommendation in relation to vaccinating the elderly against herpes zoster with the new Shingrix® vaccine. However, according to the Health Council, the cost-effectiveness of vaccination should not exceed the commonly used reference value of €20,000 per QALY, which is not the case at the current vaccine price.

9.4.2 Tables and figures

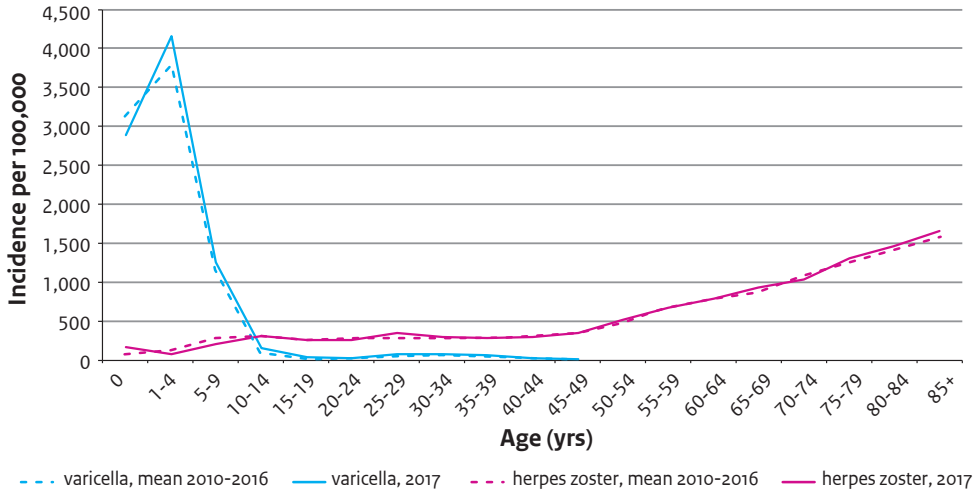


Figure 9.4.1 Estimated incidence per 100,000 population of episodes of varicella (ICPC-code A72) and herpes zoster (ICPC-code S70) in 2017 versus mean 2010-2016 by age group [1]

Note: Varicella cases in people over 49 years of age are only sporadically reported by GPs and 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 (2005–2011) and new method (2010–2017) (rounded off to closest ten)

Syndrome	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Varicella*	190	300	210	(160)	(110)	(180)							
Varicella**	130	260	230	290	180	210	230						
Varicella***						310	270	250	280	270	250	240	280
Herpes zoster**	350	370	310	340	360	360	360						
Herpes zoster***						480	490	510	510	530	530	530	530

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

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), 2005–2017 [4]

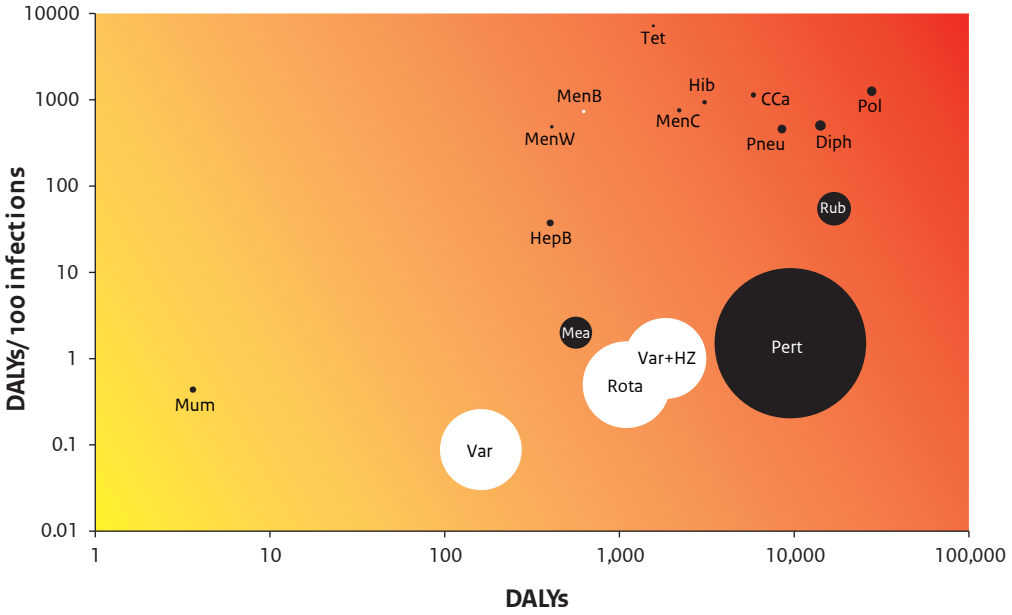
Syndrome	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015*	2016*	2017*
Varicella	1.5	1.9	1.4	1.7	1.5	1.9	1.7	1.5	1.7	1.9	1.9	2.1	2.0
Herpes zoster	2.2	1.9	2.0	2.0	2.4	2.1	2.2	2.1	2.1	2.7	3.0	2.9	2.9

Notes:
In 2006/2007, a number of hospitals ceased registration, causing an underestimation of hospital admissions from 2006 onwards till 2014 (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.
* Data rounded off to closest five. Corrected for non-participating hospitals. Data retrieved from Statistics Netherlands, this may have resulted in a trend break compared to previous years.
Source: DHD, CBS

Table 9.4.3 Absolute number of deaths with varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02) as primary cause of death, 2005–2018 [5]

Syndrome	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018*
Varicella	1	3	5	0	1	2	1	2	1	2	2	4	3	2
Herpes zoster	15	24	21	14	20	25	20	21	21	26	33	27	33	36

* Preliminary data
Source: CBS



CCa: cervical cancer (human papillomavirus (HPV) -16/18), Diph: diphtheria, HepB: hepatitis B, Hib: invasive *Haemophilus influenzae* type b disease, HZ: herpes zoster, Mea: measles, MenC/W/B: invasive meningococcal C/W/B disease, Mum: mumps, Pert: pertussis, Pneu: invasive pneumococcal disease (PCV10 types), Pol: poliomyelitis, Rota: rotavirus gastroenteritis, Rub: rubella, Tet: tetanus, Var: varicella.

Figure 9.4.2 Ranking of vaccine-preventable diseases by estimated disease burden (expressed in DALYs) at population and individual levels in the year before introduction of vaccination into the National Immunisation Programme or in 2017, the Netherlands, 1952–2017 [6].

DALY=disability-adjusted life year.

Both axes are on a logarithmic scale. Black bubbles represent estimates for the year before inclusion in the National Immunisation Programme (NIP). White bubbles represent estimates for 2017 for potential NIP candidates. The area of each bubble is proportional to the average number of estimated cases (250 cases were added to each bubble for visibility reasons). The gradient colouring from the lower left quadrant to the upper right quadrant is used to indicate different levels of burden of disease (yellow: relatively low burden at population and individual level, i.e. mumps; red: relatively high burden at population and individual level, i.e. poliomyelitis); see manuscript and Supplement 1 for all assumptions and limitations [6].

9.4.3 Epidemiology

The VZV epidemiology in the Netherlands is comparable to that in previous years (Tables 9.4.1, 9.4.2 and 9.4.3). In 2017, general practitioners recorded about 48,000 varicella and 90,000 herpes zoster episodes (280 and 530 episodes per 100,000 population respectively). The incidence of general practitioner consultations due to varicella episodes per 100,000 population is highest in children aged under five, whereas the incidence of general practitioner consultations due to 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); this new method has recently been published [7]. 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 [8]. 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 2018, we would expect 4.3 deaths (range 1.7–6.5) instead of the 36 deaths reported in 2018 (Table 9.4.3).

9.4.4 Research

In a recent analysis, we assessed the national burden of disease (BoD) of varicella and compared it to the BoD of other vaccine-preventable diseases before introduction of vaccination in the NIP. The BoD was expressed in disability-adjusted life years (DALYs) using methodology from the Burden of Communicable Diseases in Europe (BCoDE) project. In 2017, the estimated BoD of varicella - including HZ - in the Netherlands was 1,800 (95% uncertainty interval (UI): 1,800–1,900) DALYs per year. HZ mainly contributed to this BoD (1,600 DALYs; 91%), which was generally lower than the BoD of most current NIP diseases in the year before their introduction into the NIP. However, the estimated annual BoD for varicella was higher than for rotavirus gastroenteritis (1,100; 95%UI: 440–2,200 DALYs) and meningococcal B disease (620; 95%UI: 490–770 DALYs), two other potential NIP candidates (Figure 9.4.2) [6].

We investigated the immune responses after HZ vaccination (Zostavax®) in Dutch middle-aged adults. Robust short-term VZV-specific IgG antibodies were observed post vaccination. Enhancement of VZV-specific IgA as well as long-term enhancement of VZV-specific T-cell immunity was observed only in participants with low pre-vaccination immunity. Improved assays to measure T-cell immunity to VZV are in development to be able to study this in different age groups of the Dutch population.

9.4.5 International developments

9.4.5.1 Varicella

Povey et al. assessed the 10-year vaccine efficacy of two doses of a combined measles-mumps-rubella-varicella vaccine (MMRV) or one dose of a monovalent varicella vaccine (V) given after a MMR vaccine (MMR+V) compared with two MMR doses. Vaccine efficacy against all varicella was 95.4% (95%CI: 94.0–96.4%) for MMRV and 67.2% (95%CI: 62.3–71.5%) for MMR+V. For moderate or severe varicella, the efficacy was 99.1% (95%CI: 97.9%–99.6%) for MMRV and 89.5% (95%CI: 86.1–92.1%) for MMR+V [9]. In Australia, the single-dose infant varicella vaccination programme with Varilrix® has an estimated effectiveness of 64.7% (95%CI: 43.3–78.0%) against hospitalisation due to varicella [10]. In the Veneto region of Italy, the adjusted direct effectiveness of a single dose of ProQuad® against varicella of any severity was 94% (95%CI: 91–95%) [11]. In Madrid, the overall VE of a single-dose vaccination (Varivax®) against varicella was estimated at 93.1% (95%CI: 90.9–94.8%) using the screening method, and at 92.4% (95%CI: 80.8%–97.0%) using a case-control study [12]. An updated analysis for the United States showed that the annual average mortality rate for varicella in 2012–2016 declined by 94% compared with the pre-vaccine period (1990–1994) and by 47% compared with the end of the one-dose varicella vaccine period (2005–2007) [13].

An assumption-based analysis suggested that the risk of febrile convulsions following a first dose of MMRV could be reduced by administering the vaccine only to children with no personal or family history of febrile convulsions. Children with a personal or family history of febrile convulsions could be vaccinated with separate but concomitant MMR+V vaccines [14].

Toyama et al concluded that universal varicella vaccination in Japan (introduced in 2014) has increased the incidence of HZ, mostly in those aged 20–29 years, the child-rearing generation [15]. These results and conclusion are remarkable as the potential effect of varicella vaccination on zoster incidence is expected to occur several decades later in time. Zoch-Lesniak et al showed a decrease in HZ incidence in children after introduction of varicella vaccination in Germany but an increase in HZ incidence in adults. Whether this increase in adults is associated with varicella vaccination in children remained unclear [16]. Harpaz & Leung and Wolfsen also reported a decrease in HZ incidence in children and an ongoing increase in HZ incidence in adults in the US but with a deceleration of the increase among older adults [17-19].
A review by Varela et al. concluded that there is no definite and consistent association between childhood varicella vaccination and the increase in HZ incidence in the elderly. Furthermore, a shift of varicella disease to older age has not been confirmed. Several studies have reported an overall decrease in the incidence of varicella, also among older age groups. Most studies with a longer follow-up showed a reduction >80% in the incidence of varicella and hospitalisations. Indirect protection of individuals not eligible for varicella vaccination (children too young to be vaccinated, susceptible pregnant women and immunocompromised individuals) has also been reported [20]. Multiple other reviews also stated that real-world evidence has not confirmed the model-predicted increase in HZ incidence after varicella vaccination; the rising HZ incidence that was already observed before the introduction of varicella vaccination may be the result of declining birth rates and/or ageing populations [21-24]. An explanation for the divergence between previous projections of HZ incidence after varicella vaccination and real-world incidence may be that endogenous boosting compensates when exogenous boosting declines [24, 25].

9.4.5.2 Herpes zoster

In a previous advisory report issued in 2016, the Health Council of the Netherlands concluded that HZ vaccination did not qualify for a national programme, mainly due to insufficient protection, including low vaccine efficacy and limited duration of protection, of the only available vaccine (Zostavax®) at the time. Furthermore, the vaccine was not suitable for immunocompromised individuals [26]. Due to the availability of the new Shingrix® vaccine, the Health Council published a new advisory report on vaccination against HZ in July 2019. In principle, the Health Council issued a positive recommendation with regard to vaccinating the elderly against HZ with this new vaccine. However, the disease burden of HZ is relatively low compared to that of other diseases, such as pneumococcal disease and influenza. The Health Council therefore considers it important that the cost-effectiveness of vaccination does not exceed the commonly used reference value of €20,000 per QALY. To achieve that goal, the price of the vaccine should be reduced considerably [27].
In England, the estimated overall vaccine effectiveness of Zostavax® against HZ was 66.8% (95%CI: 62.2–71.0%) for subjects born in 1943–1946 (routine cohorts) and 1934–1937 (catch-up cohorts). A lower vaccine effectiveness was found in diabetics and in individuals with a history of HZ [28]. Another study in the United Kingdom found a vaccine effectiveness of 65.3% (95%CI: 60.3–69.6%) against HZ and 71.6% (50.0–83.9%) against PHN [29].

Two reviews by Tricco et al. and McGirr et al. confirmed once again that Shingrix® is significantly more effective than Zostavax® in reducing the incidence of HZ and PHN in adults. Furthermore, Shingrix® is more reactogenic than Zostavax® [30, 31].

A phase 3, randomised, observer-blinded study among 1,846 adult autologous hematopoietic stem cell transplantation (HSCT) recipients showed that a two-dose schedule of Shingrix® significantly reduced the incidence of HZ over a median follow-up of 21 months, although the estimated vaccine efficacy of 68.2% [32] was lower than in non-transplant populations aged 50 years or older (91%) [33, 34].

9.4.5.3 Cost-effectiveness

In Italy, since 2017, varicella vaccination in a two-dose schedule has been introduced nationally for all newborns as one of the ten vaccines that have become compulsory for school attendance. A live attenuated vaccine against HZ has been recommended for adults aged 65 and older. In an economic evaluation the combination of the two vaccinations has been evaluated, taking into account new demographic figures and two different underlying mechanisms of exogenous boosting (temporary and progressive immunity) [35]. Demographic processes have contributed to shaping varicella and HZ epidemiology over the years, decreasing varicella circulation and increasing the incidence of HZ in the short term. Under the assumption of progressive immunity, combined vaccination would lead to a decline of 435,000 undiscounted cases of varicella and more than 77,000 cases of HZ (and 81 HZ-related deaths) per year at a cost of €4,375 per QALY gained. An additional catch-up campaign for HZ vaccination targeting people aged 66–75 would further increase the benefits of the combined programme, leading to an additional reduction of 3,542 cases of HZ and 6 HZ-related deaths per year at a cost of €6,829 per QALY gained.
In the United States, HZ vaccination is recommended for adults aged 60 years and older. Curran et al. compared the cost-effectiveness of an adjuvanted Recombinant Zoster Vaccine (RZV, Shingrix®), with a no-vaccination strategy and the live attenuated HZ vaccine (Zoster Vaccine Live (ZVL), Zostavax®). The Incremental Cost-Effectiveness Ratio (ICER) of RZV compared with no vaccination was $11,863 per quality-adjusted life-year (QALY) gained from a societal perspective. Compared to ZVL, a vaccination strategy with RZV would be cost-saving [36]. Curran et al. also estimated the cost-effectiveness of RZV vaccination among older adults in the United States who have been previously vaccinated with ZVL. They showed that vaccination with RZV five years after previous vaccination with ZVL would result in an ICER of $58,793 per QALY saved compared with no additional vaccination [37].
The cost-effectiveness of RZV compared with no vaccination was also assessed for the Japanese and German older population. In Japan, the ICERs for vaccinating adults of 65 years or older with RZV with no vaccination were approximately ¥4,320,000 (around €33,000) and ¥4,040,000 (around €31,000) per QALY gained from a payer's and the societal perspective, respectively [38]. In Germany, the ICER was estimated at approximately €37,000 and €44,000/QALY for the age cohorts ≥60 and ≥70 years of age, respectively [39]. All these studies were funded by GlaxoSmithKline Biologicals SA [36-39].

The cost-effectiveness of vaccination with RZV compared with ZVL and no vaccination was evaluated by Prosser et al [40]. The target population was a hypothetical cohort of immunocompetent US adults aged 50 years or older. For vaccination with RZV compared with no vaccination, ICERs ranged by age from $10,000 to $47,000 per QALY, using a societal perspective and assuming 100% completion of the two-dose RZV regimen. Vaccination with ZVL was dominated by vaccination with RZV for all age groups 60 years or older. Vaccination with RZV after previous administration of ZVL yielded an ICER of less than $60,000 per QALY for persons aged 60 years or older.

New health technologies are more likely to be adopted when they have a lower ICER and/or when their ICER is presented with more certainty. Industry-funded (IF) health economic evaluations often use more favourable base-case values, leading to more favourable conclusions. Bilcke et al. reviewed health economic evaluations of varicella-zoster virus vaccination in the elderly and studied base case values and uncertainty in IF and non-industry-funded (NIF) evaluations [41]. Despite using the same data sources, IF studies (n = 10) assume a longer duration of vaccine protection, have a higher percentage of HZ patients developing postherpetic neuralgia, and tend to use higher HZ utility loss than NIF studies (n = 11) for their baseline. IF studies show lower ICERs given similar or even higher vaccine prices than NIF studies, assume lower uncertainty around the duration of vaccine protection, and tend to use lower uncertainty around the duration of postherpetic neuralgia. Yet their quality has been rated equally well using current standard quality rating tools. Researchers and decision-makers should be aware of potential sponsorship bias in health economic evaluations, especially in the way source data are used to specify base-case values and uncertainty ranges.

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 table 10.1 below. Vaccine development takes 10-15 years, 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 are described in earlier chapters.

Table 10.1 Vaccines in the clinical testing phase and relevant for the Netherlands

Pathogen	Vaccine	Status, clinical phase
Bacteria		
Chlamydia	Adjuvanted chlamydia vaccine CTH522 (SSI)	I (second phase I)
Clostridium difficile	Toxoid inactivated	FDA fast track (Sanofi Pasteur ended its programme, Pfizer Phase III trial ongoing)
	Recombinant toxoid 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)	II (fast track FDA)
Meningococcal ABCWY	MenABCWY recombinant conjugated Novartis/GSK,	II adolescents
	Pfizer	I

Pathogen	Vaccine	Status, clinical phase
Moraxella catarrhalis, non-typeable Haemophilus influenza COPD	Recombinant COPD reduction with adjuvant (GSK)	II
Shigella	-Live attenuated single-strain,	I completed
	-Inactivated trivalent whole cell,	II
	-Chemical glycoconjugate	I
	-Rrecombinant 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

Pathogen	Vaccine	Status, clinical phase
Streptococcus group A & B	-Group A: N-terminal M protein-based multivalent vaccines (26-valent and 30-valent)	II
	Conserved M protein vaccines (the J8 vaccine and the	I
	StreptInCor vaccine) C-terminal M-protein DTconjugate, AlOH adj.	 I
	-Group B: CPS-protein conjugate (mono and trivalent) (GSK)	II maternal
	6-valent polysaccharide CRM197 conjugated vaccine (Pfizer)	I/II maternal
	Recombinant fusion antigen Minervax APS	I
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

Pathogen	Vaccine	status
Viruses		
Chikungunya	Live recombinant Measles Virus based Virus-like particle (NIAID)	II, Immunogenic and safe in adults
	Live attenuated (Valneva)	I FDA fast track
Cytomegalo (CMV)	-Glycoprotein B bivalent	I and III
	-DNA (Astellas/ Vical)	III failed CMV+ stem cell transplant patients
	-Replication defective V160 (MSD)	II
	-Stem cell transplant patients (Merck)	Approved US 2017
Dengue	-Live recombinant (tetravalent) (Butantan/NIAID)	III
	-Live-attenuated (tetravalent) TDV (Takeda)	III
	-Inactivated (tetravalent) V180(Merck)	I
	-Recombinant subunit (tetravalent) (GSK)	I/II
	-Monovalent subunit DNA	Dengvaxia Sanofi registration approved for 9-45 years of age
Ebola	-rVSVΔG-ZEBOV-GP V920 (Merck/ NewLink Genetics)	III, approved for compassionate use
	-CAd3-EBOZ (GSK/NIH/NIAID)	III
	-Ad26-EBOV and MVA-EBOV (Johnson & Johnson/Janssen vaccines and Bavarian Nordic)	I
	-Recombinant nanoparticle based (Novavax)	III
	-Recombinant viral vector (GSK)	II
	-VRC-EBOADC069-00-VP (Okairos, NIAID)	I

Pathogen	Vaccine	status
Epstein–Barr	Recombinant gp350 Glycoprotein subunit	II
	Live attenuated vaccines	On hold
Hepatitis C	Recombinant, heterologous viral vector (GSK)	II
Hepatitis E	Recombinant protein	IV, (Hecolin®, Xiamen China Approved in China not registered in EU)
Herpes simplex	-HSV-529 replication defective live attenuated (Sanofi)	I
Herpes zoster (Shingles)	Recombinant (Shingrix, GSK)	Approved US and EU
	Inactivated V212 (Merck)	III, on hold
HIV	Recombinant protein (GSK)	II
	Viral vector Prime/boost (Sanofi)	II
	Ad26 Mos HIV vaccine (Janssen vaccines)	III
	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 Scinence/ Inovio)	II
Parainfluenza type I	Live attenuated	I-II
Pneumococcocus	(killed) whole cell vaccine	II
	Protein-based vaccines (GSK, Sanofi)	I, II

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

Source: WHO and clinicaltrial.gov, websites of pharmaceutical companies.

List of abbreviations

4CMenB	multicomponent meningococcal B vaccine
9vHPV	nonavalent HPV-vaccine
ACIP	Advisory Committee on Immunisation Practices
AE	adverse events
AEFI	adverse events following immunisation
aP	acellular pertussis
ARI	acute respiratory infections
BCG	Bacillus Calmette-Guérin
BIGSdb	Bacterial Isolate Genome Sequence Database
BLNAR	beta lactamase negative ampicillin resistant
bOPV	bivalent oral polio vaccine
CAP	community acquired pneumonia
CBA	cost-benefit analysis
CBS	Statistics Netherlands
Cc	clonal complex
CDC	Centres for Disease Control and Prevention
CFR	case fatality rate
CFS	chronic fatigue syndrome
cgMLST	core genome Multi Locus Sequence Typing
CI	confidence interval
CIb	Centre for Infectious Disease Control
CIN	cervical intraepithelial neoplasia
CMV	Cytomegalovirus
COPD	chronic obstructive pulmonary disease
CRM	CRM conjugate
CRPS	complex regional pain syndrome
CSF	cerebrospinal fluid
DALY	Disability Adjusted Life Years
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-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
EMA	European Medicines Agency
EU/EEA	European Union / European Economic Area
F	fusion
FDA	Food and Drug Administration

FHA	filamentous haemagglutinin
FinIP	Finnish Invasive Pneumococcal disease
Fim3	serotype 3 fimbriae
FU	Follow-up
GAPIII	the WHO global action plan to minimise poliovirus facility-associated risk
GBD	Global Burden of Disease
GBS	Guillain-Barre syndrome
GE	gastroenteritis
GMC	geometric mean concentrations
GMT	geometric mean titres
GP	General Practitioner
GPLN	WHO Global Polio Laboratory Network
GSK	Glaxo Smith Kline
GW	genital warts
HAV	hepatitis A virus
HAVANA	Study of HPV prevalence among young girls
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	healthcare professionals
HepB	hepatitis B virus
Hib	*Haemophilus influenzae* type b
Hie	*Haemophilus influenzae* type e
Hif	*Haemophilus influenzae* type f
HIV	human immunodeficiency virus
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
HSCN	Health Study Caribbean Netherlands
HSV	herpes simplex virus
HZ	herpes zoster
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
ICPC	International Classification of Primary Care
ICU	intensive care unit
IDS	Centre for Infectious Disease Research, Diagnostics and Screening
IDU	injecting drug use
IgG	immunoglobulin G
IgM	immunoglobulin M
ILI	influenza-like illness
IMD	invasive meningococcal disease
IPD	invasive pneumococcal disease
IPV	inactivated polio vaccine

IR	incidence rate
IU/ml	international units per millilitre
LBZ	National Register Hospital care
LINH	the Netherlands Information Network of General Practice
LMR	National Medical Registration
lrHPV	low-risk human papillomavirus
MATS	the meningococcal antigen typing system
MC	MLVA complex
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-TT	Meningococcal serogroup C polysaccharide-tetanus toxoid
MenW	Meningococcal serogroup W
MenY	Meningococcal serogroup Y
MERS-CoV	Middle East Respiratory Syndrome-coronavirus
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
MST	minimum spanning tree
MSM	men who have sex with men
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
NKR	the Netherlands Cancer Registry
NPG	National Influenza Prevention Programme
NPL	National Polio Laboratory
NLRBM	Netherlands Reference laboratory for Bacterial Meningitis
NTHi	nontypeable *Haemophilus influenzae* strains
NTM	neurotrimin
OP	oropharyngeal
OPV	oral polio vaccine
OR	odds ratio
PASSYON	Papillomavirus Surveillance among STI clinic Youngsters
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PCV7	heptavalent pneumococcal conjugate vaccine
PCV10	10-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
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
PPV23	23-valent pneumococcal polysaccharide vaccine
PPV23-PCV13	additional types in PCV13 compared to PPV23
Prn	pertactin
PRP	polyribosyl-ribitol-phosphate
Ptx	pertussis toxin
QALY	quality-adjusted life year
qPCR	real-time polymerase chain reaction
RIVM	National Institute for Public Health and the Environment, the Netherlands
RSV	respiratory syncytial virus
RV	rotavirus
SHC	sexual health centres
SLE	systemic lupus erythematosus
SPR	RIVM strategic programme
STI	sexually transmitted infections
Tdap	tetanus, diphtheria and pertussis vaccine
TT	tetanus toxoid
UK	United Kingdom
US	United States
VDPV	vaccine-derived poliovirus
VE	vaccine effectiveness
VLP	virus-like particle
VPD	vaccine-preventable disease
VZV	varicella zoster virus
wgMLST	whole-genome multi locus sequence type
WGS	whole genome sequencing
WHO	World Health Organization
wP	whole-cell pertussis
WPV	wild poliovirus
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, under-reporting and a delay in reporting are issues with regard to several diseases [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 GGD in question reports cases to RIVM through the online OSIRIS platform. 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 procedure 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 Prismant research institute in the National Medical Register (LMR). After 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 amounted to about 99% until mid-2005. Thereafter, coverage has 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, causing an underestimation of hospital admissions from 2006 onwards till 2014. 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 retrieved from Statistics Netherlands. These data are corrected for non-participating hospitals, this may have resulted in a trend break compared to previous years. Due to privacy, data are also rounded off to closest five. With these numbers one should take into account that 0 cases is not always actually 0, but can also be a few cases.

Table A1.2 The completeness of LMR/LBZ data through 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 are corrected for non-participating hospitals
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 programme is based primarily 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 virological laboratories yields insights into the number of positive RSV tests, reflecting RSV circulation. These specimens are collected mainly 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 that are members 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 data. 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. 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 disease 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 resulting in a more reliable denominator [14, 15]. Because of these changes, we decided to report previously published incidence rates until 2011 based on the old method [16] and incidence rates from 2012 onwards using the new method [17]. Due to the new estimation method, the data for 2012 (based on 219 practices) and onwards are not comparable with that for previous years.

A1.1.2 Methods for disease surveillance

A1.1.2.1 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 [18, 19].

A1.1.2.2 Impact of implementation of vaccination

The impact of vaccination (programmes) 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 programme, 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 programme.

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 [20]. A specific type of case-control design used to estimate VE is the indirect cohort design or Broome method [21]. 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 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 [22]. 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 [23]. 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.

A1.1.2.4 Pertussis vaccination coverage

Previously, to calculate the vaccine effectiveness for the pertussis booster vaccination at 4 years old, a standardised vaccination coverage estimate of 92% was used for the PPV. In response to the recent changes in vaccination coverage, the PPV has been adjusted by birth cohort this year. For each birth cohort, the vaccination coverage as reported in the national vaccination coverage report 2018 was used. This resulted in a different PPV for each birth cohort, and a more accurate VE calculation.

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 fill in a questionnaire (PIENTER survey). This survey was performed in 1995-1996 (N_{blood}=10,128) [24],

2006–2007 (N_{blood}=7,904) [25], and 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) [26].

A1.4.1 Maternal pertussis vaccination coverage

The maternal pertussis vaccination is not registered in Præventis, because it has not yet been introduced in the NIP yet. To estimate maternal pertussis vaccination coverage, vaccination data of women in the fertile age group (20-45 years) were collected from the national apothecaries (SFK) and the municipal health services. Data were received from 20 out of the 5 municipal health services. We decided not to correct for the missing municipal health services, as this could easily result in an overestimation of the vaccine coverage.
The number of administered vaccinations of the SFK data and municipal health services that provided monthly data was added together to create the graph with the monthly trend. Due to differences in data registration, some municipal health services were able to provide only numbers per year. These were used to calculate the mean vaccination coverage of each year, but were not used in the figure. This explains why the mean vaccination coverage is higher than the coverage depicted in figure 7.8.5.
To ensure that we did not overestimate number of administered maternal vaccinations, an approximate baseline number of vaccinations was subtracted from the total number of vaccinations. This baseline consisted of three approximate numbers: 1. the vaccinations given before the maternal vaccination was available, 2. the vaccinations related to travel, and 3. the vaccinations related to healthcare professions.
The first number was obtained by looking at the number of vaccinations administered at the beginning of 2016, as reported in the SFK data. The second number was obtained by counting the travel-related vaccinations as reported by the municipal health services. When a person comes for a travel-related vaccination, the country of destination is reported. Finally, the third number was obtained by looking at the number of pertussis vaccinations administered in 45-to 69-year-olds. These women are less likely to be vaccinated because of a pregnancy, and could be used as a proxy of the healthcare-related vaccinations.
To get an approximation of the number of pregnant women in 2018 and the first three months of 2019, the annual number of pregnant women as reported by Perined in 2017 was used [27]. The number of pregnant women in 2017 was 163,826. For 2019, this number was divided by four, as we only had data up to 1 April for the SFK data, and 1 March for the municipal health services data. To create the graph of the monthly trend, the annual number of pregnant women was divided by 12.

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 [28].

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 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. In January 2017, the procedure for registering AEFIs in the Lareb database was changed. Previously, reports of redness, swelling, pain and warmth at the injection site were recorded as injection-site inflammation. Since January 2017, these local reactions are registered separately. As a result, the number of AEFIs per report is higher.
In addition, the Centre for Infectious Disease Control (CIb) of 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 year (QALY), which is a measure of disease burden comprising both the quality and 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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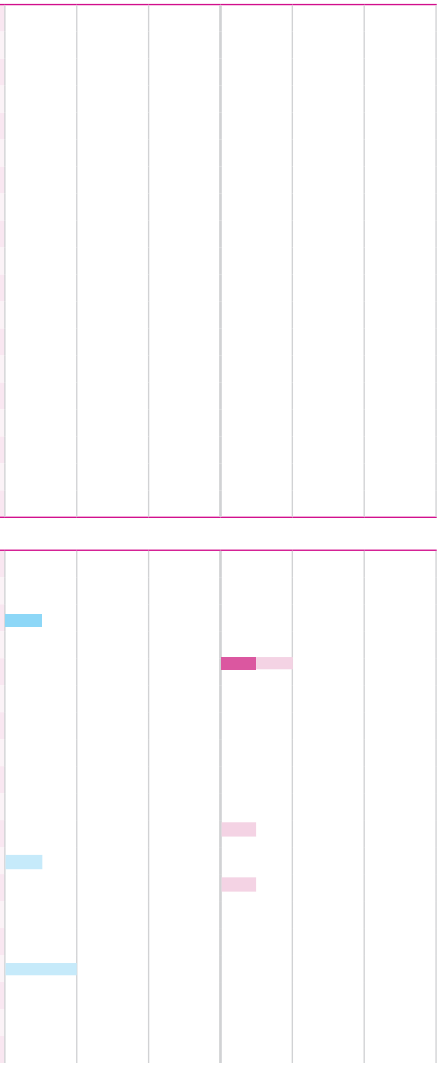
* RIVM publication

Appendix 2 Morbidity and mortality figures

Diseases included in the current NIP

Diphtheria								ICD10: A36
Year	Age (years)						Total	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)								
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**	
2018*	0	0	0	0	0	0	**0**	
*Hospitalisations** (source: Prismant/DHD/CBS)*								
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**	
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 statistical year 2013 onwards, the coding of causes of death is partly automatic.

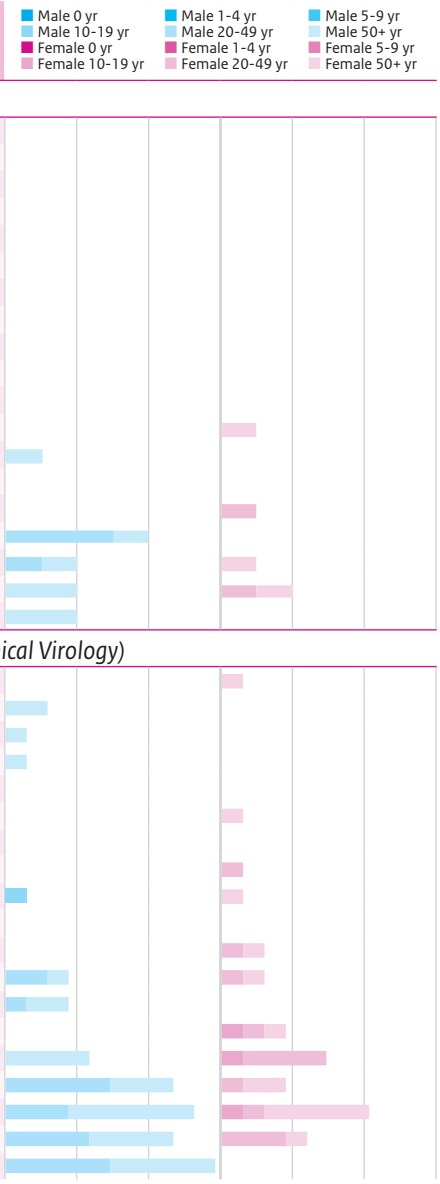
**Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases is not always actually 0, but can also be a few cases.

Diphtheria

ICD9: 032
ICD10: A36

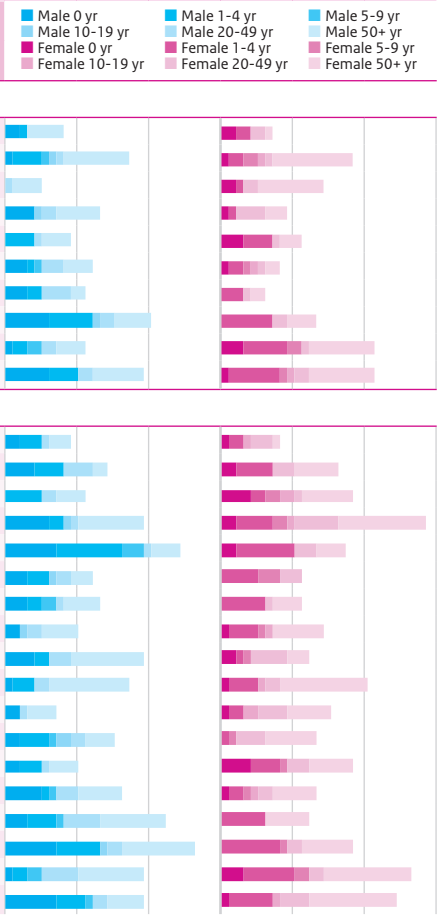
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Notifications (source: Osiris)							
2000	0	0	0	0	0	0	**0**
2001	0	0	0	0	0	0	**0**
2002	0	0	0	0	0	0	**0**
2003	0	0	0	0	0	0	**0**
2004	0	0	0	0	0	0	**0**
2005	0	0	0	0	0	0	**0**
2006	0	0	0	0	0	0	**0**
2007	0	0	0	0	0	0	**0**
2008	0	0	0	0	0	0	**0**
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**
2018	0	0	0	0	0	2	**2**
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**
2018	0	0	0	0	5	5	**10**



*Number of diphtheria isolates.

Haemophilus influenzae

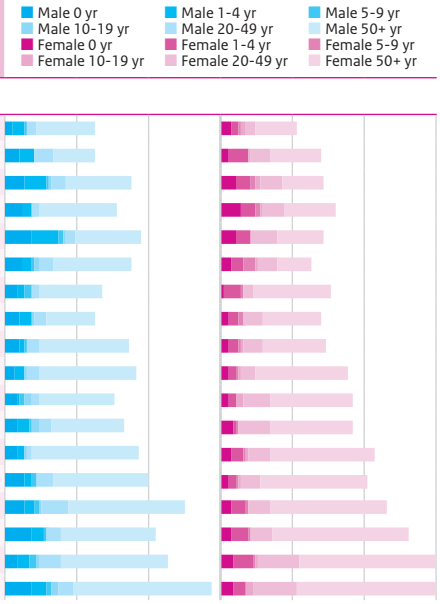
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Notifications (serotype b; source: Osiris)*							
2009	4	3	0	0	2	6	**15**
2010	2	6	3	2	2	20	**35**
2011	2	1	0	0	3	13	**19**
2012	5	1	0	1	6	9	**22**
2013	3	8	0	0	2	7	**20**
2014	4	3	2	1	4	6	**20**
2015	3	5	0	0	5	4	**17**
2016	6	13	0	1	4	9	**33**
2017	4	8	4	0	3	13	**32**
2018	7	11	1	1	4	16	**40**
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**
2018	8	10	1	1	6	17	**43**



*Notifiable since 2009

Haemophilus influenzae

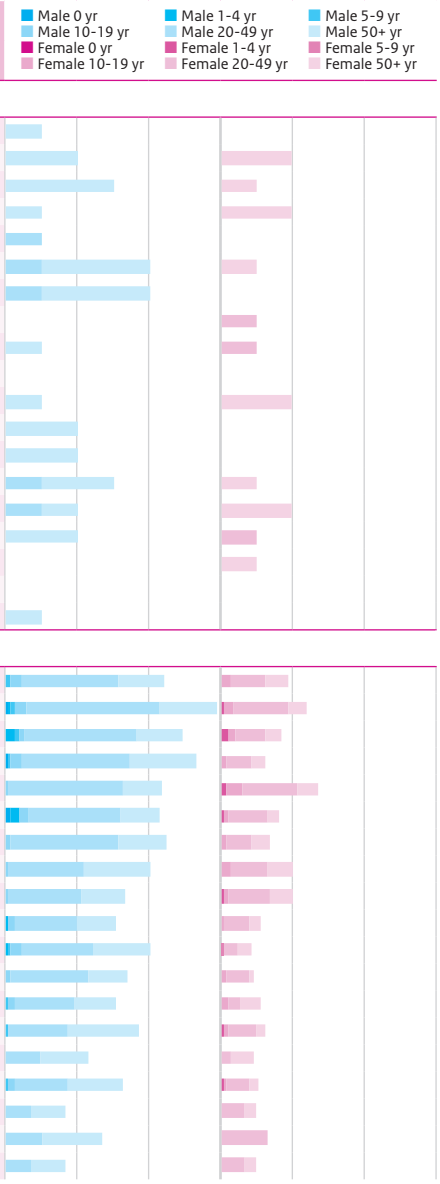
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Laboratory diagnoses (all serotypes; source: NRLBM)							
2001	9	13	2	3	11	55	**93**
2002	13	18	0	2	22	53	**108**
2003	21	19	5	4	20	60	**129**
2004	19	14	2	3	15	72	**125**
2005	21	24	3	1	19	64	**132**
2006	14	12	8	4	21	61	**120**
2007	7	14	5	1	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**
2018	21	15	3	8	32	157	**236**



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)							
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**
2018*	0	0	0	0	0	1	**1**
*Hospitalisations** (source: Prismant/DHD/CBS)*							
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**
2015^	0	0	0	0	20	20	**40**
2016^	0	0	0	0	30	25	**60**
2017^	0	0	0	0	20	20	**40**



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

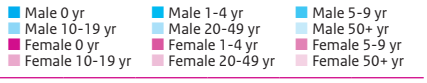
**Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases is not always actually 0, but can also be a few cases.

**Age is unknown for 18 patients.

Hepatitis B

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	



Notifications (Acute; source: Osiris)

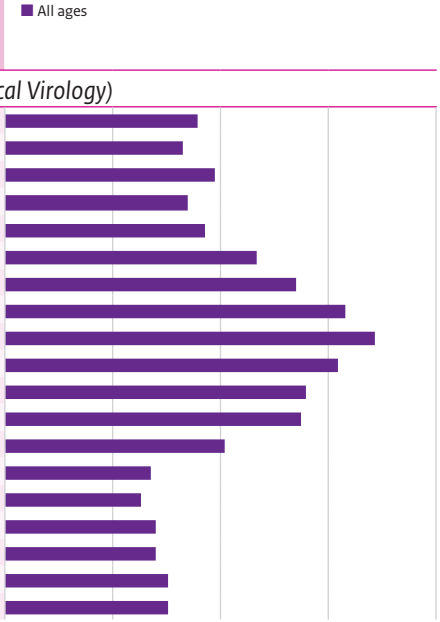
2000	0	3	1	31	186	26	**247**
2001	0	0	2	23	163	33	**221**
2002	0	0	0	22	193	44	**259**
2003	0	1	3	22	240	56	**322**
2004	0	1	0	15	240	40	**296***
2005	0	0	2	26	227	46	**301**
2006	0	0	0	20	166	56	**242**
2007	0	1	1	20	154	50	**226**
2008	0	0	1	13	170	41	**225**
2009	0	0	0	11	144	56	**211**
2010	0	0	0	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**
2018	0	0	0	2	64	38	**104**

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**
2018	0	0	0	40	746	244	**1,030**

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)							
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							**760**
2018							**764**



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)								
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**	
2018*	0	0	0	0	50	167	**217**	
Registrations (cervical cancer; source NKR)								
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	429	337	**766**	
2018**	0	0	0	0	472	360	**832**	

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

**Preliminary figures

Measles								ICD10: B05
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)								
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**	
2018*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
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**	
2018	3	4	0	2	14	1	**24**	

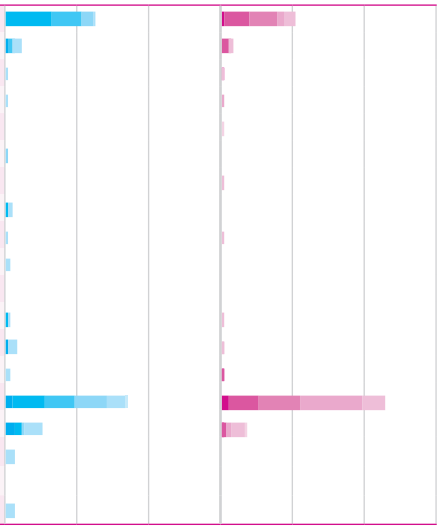
*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

Measles

ICD9: 055
ICD10: B05

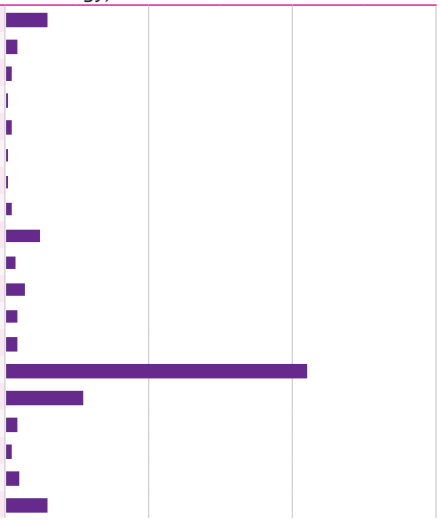
Hospitalisations (source: Prismant/DHD)*

Year	Age (years) 0	1-4	5-9	10-19	20-49	50+	Total
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**
2015^	0	0	0	0	5	0	**5**
2016^	0	0	0	0	0	0	**0**
2017^	0	0	0	0	5	0	**5**



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

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**
2018	**29**



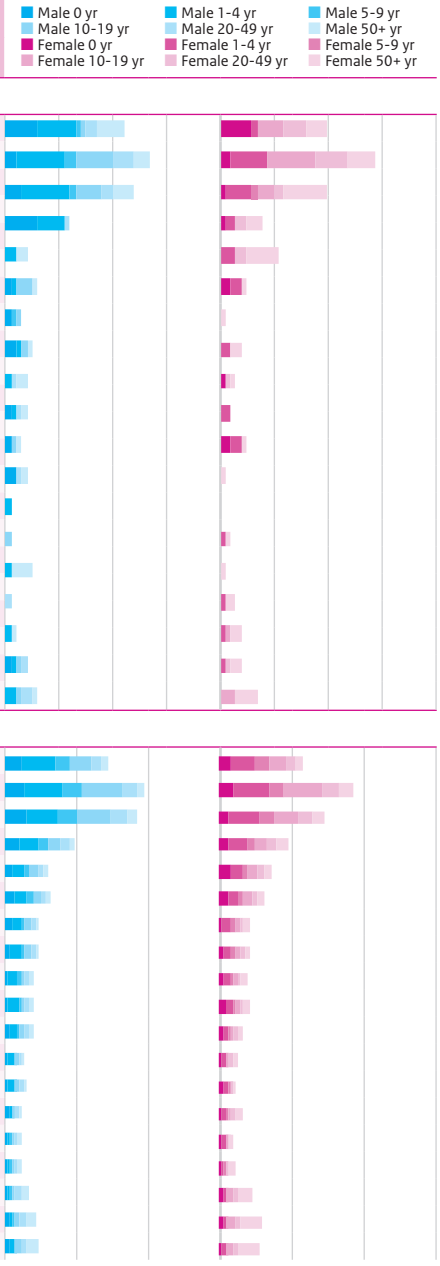
*Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases is not always actually 0, but can also be a few cases.

*Age is unknown for six patients.

Meningococcal disease — ICD10: A39

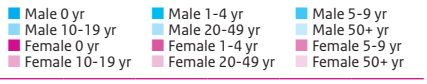
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
1997	7	13	6	6	2	7	**41**
1998	10	19	2	10	2	9	**52**
1999	9	13	4	7	4	11	**48**
2000	12	8	1	6	6	9	**42**
2001	4	16	2	16	10	8	**56**
2002	4	14	2	8	4	12	**44**
2003	7	7	0	0	3	3	**20**
2004	0	5	0	0	2	8	**15**
2005	3	3	0	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**
2018*	0	2	0	4	2	5	**13**
Notifications (source: Osiris)							
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**
2018	16	25	2	37	29	96	**205**



*Preliminary figures. From statistical year 2013 onwards, the coding of 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)

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**
2018	15	25	3	33	28	101	**205**

Laboratory diagnoses (serogroup C; source: NRLBM)

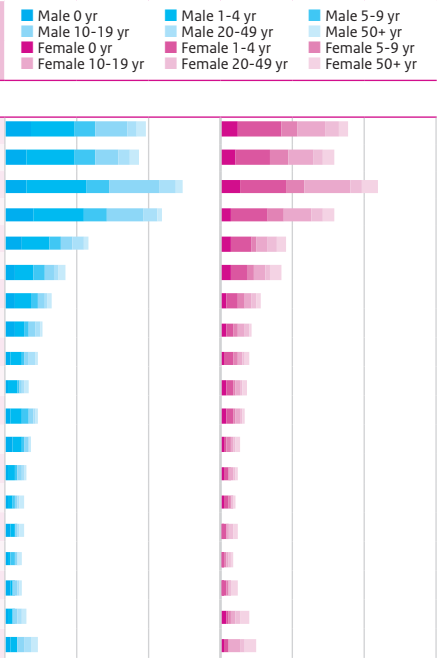
2000	2	22	16	29	19	19	**107**
2001	20	53	27	105	43	29	**277**
2002	13	39	30	73	42	25	**222**
2003	11	6	0	1	16	8	**42**
2004	1	1	1	0	7	7	**17**
2005	0	0	0	0	2	2	**4**
2006	0	1	0	0	2	1	**4**
2007	2	0	1	1	4	2	**10**
2008	2	0	0	0	4	5	**11**
2009	1	1	0	0	2	5	**9**
2010	2	0	0	2	2	0	**6**
2011	0	0	0	0	1	2	**3**
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**
2018	0	0	0	0	1	2	**3**

Meningococcal disease								ICD9: 036.0-4, 036.8-9 ICD10: A39
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+		
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**	
2018	5	3	2	16	14	63	**103**	
Laboratory diagnoses (serogroup B; source: NRLBM)								
2000	73	133	55	72	47	38	**418**	
2001	68	142	54	88	37	33	**422**	
2002	65	115	53	72	39	31	**375**	
2003	49	88	36	49	38	33	**293**	
2004	48	73	22	40	22	27	**232**	
2005	36	60	27	38	22	26	**209**	
2006	25	45	20	28	19	18	**155**	
2007	27	50	18	27	20	17	**159**	
2008	13	46	17	17	11	24	**128**	
2009	23	42	17	18	11	15	**126**	
2010	21	31	12	13	15	20	**112**	
2011	14	23	3	10	14	11	**75**	
2012	16	25	3	10	11	11	**76**	
2013	17	20	6	11	16	19	**89**	
2014	8	16	9	9	8	11	**61**	
2015	9	11	5	14	8	18	**65**	
2016	14	12	6	12	16	17	**77**	
2017	11	17	3	23	15	12	**81**	
2018	9	22	1	12	11	19	**74**	

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+	
Hospitalisations (source: Prismant/DHD/CBS)*							
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**
2015^	15	15	10	15	10	25	**90**
2016^	20	20	10	20	30	35	**135**
2017^	15	30	5	55	30	55	**190**



*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.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases is not always actually 0, but can also be a few cases.

*Age is unknown for 12 patients.

Mumps								ICD10: B26
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)								
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**	
2018*	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**	
2018	0	1	3	5	54	10	**73**	

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

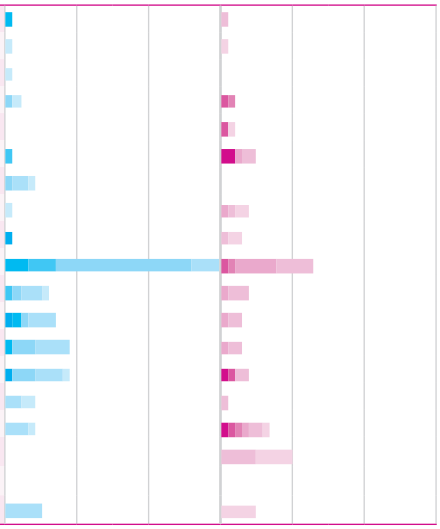
**Notifiable from 1 December 2008 onwards

Mumps

ICD9: 072
ICD10: B26

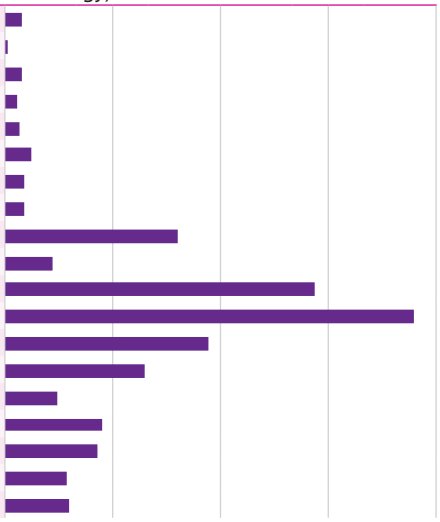
Hospitalisations (source: Prismant/DHD/CBS)*

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
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**
2015^	0	0	0	0	5	5	**15**
2016^	0	0	0	0	0	5	**5**
2017^	0	0	0	0	5	5	**10**



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

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**
2018	**30**



*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.

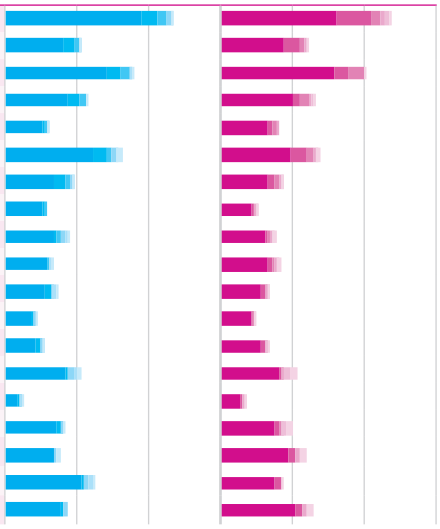
^ Data corrected for non-participating hospitals and rounded off to closest five.

*Age is unknown for one patient.

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)								
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**	
2018*	1	0	0	0	0	0	**1**	
Notifications (source: Osiris)								
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**	
2018	193	334	432	1,260	1,534	1,144	**4,897**	

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

Pertussis								ICD9: 033 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+		
Hospitalisations (source: Prismant/DHD/CBS*								
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**	
2015^	165	10	0	10	5	10	**200**	
2016^	180	15	0	5	5	10	**215**	
2017^	180	10	0	10	5	10	**215**	



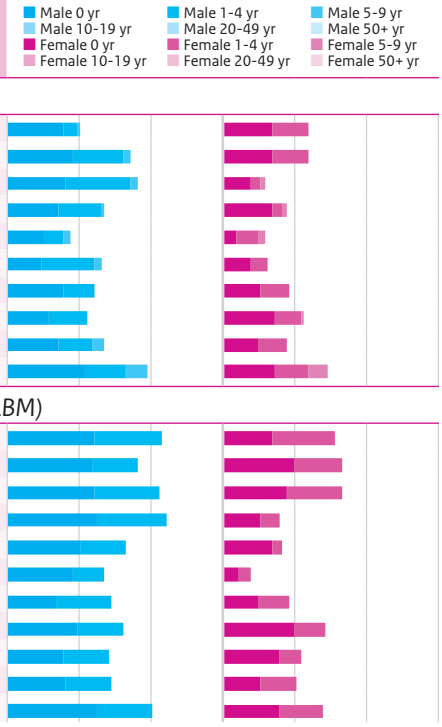
*Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases is not always actually 0, but can also be a few cases.

*Age is unknown for three patients.

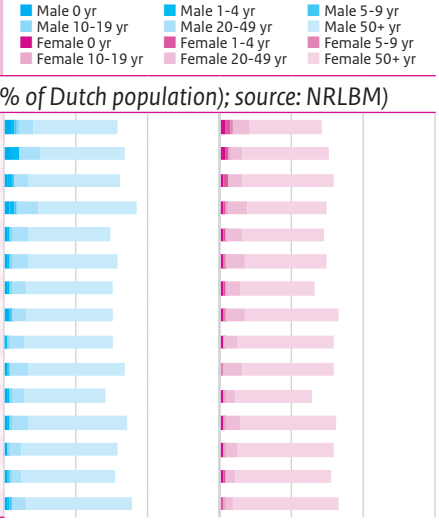
Pneumococcal disease

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**
2018	35	21	12	2			**70**
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**
2018	40	28					**68**



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**
2018	7	9	5	5	67	595	**688**
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**

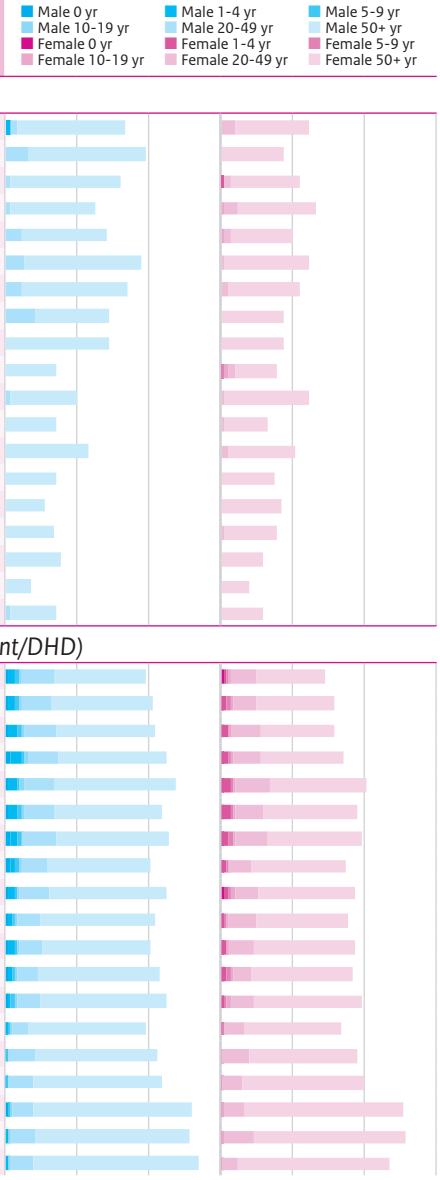


*Notifiable for 0- to 5-year-old children since 2009.

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)*							
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**
2018*	0	0	0	0	1	25	**26**
*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**
2015^	5	10	10	25	310	2,215	**2,575**
2016^	0	5	5	25	385	2,165	**2,585**
2017^	5	5	5	15	280	2,220	**2,530**



*Preliminary figures. From statistical year 2013 onwards, the coding of 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.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases is not always actually 0, but can also be a few cases.

**Age is unknown for 16 patients.

Poliomyelitis								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+		
Mortality (acute; source: CBS)								
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**	
2018*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
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**	
2018	0	0	0	0	0	0	**0**	

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

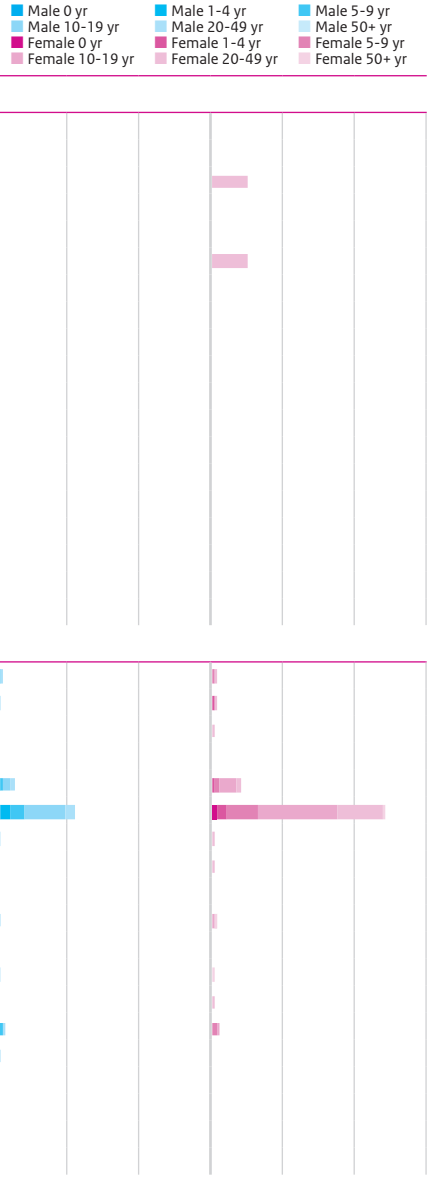
Poliomyelitis								ICD9: 045 ICD10: A80
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Hospitalisations (source: Prismant/DHD)*								
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**	
2015^	0	0	0	0	0	0	**0**	
2016^	0	0	0	0	0	0	**0**	
2017	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.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases is not always actually 0, but can also be a few cases.

Rubella (acquired) — ICD10: B06

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
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**
2018*	0	0	0	0	0	0	**0**
Notifications (source: Osiris)							
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**
2018	0	0	0	0	0	0	**0**

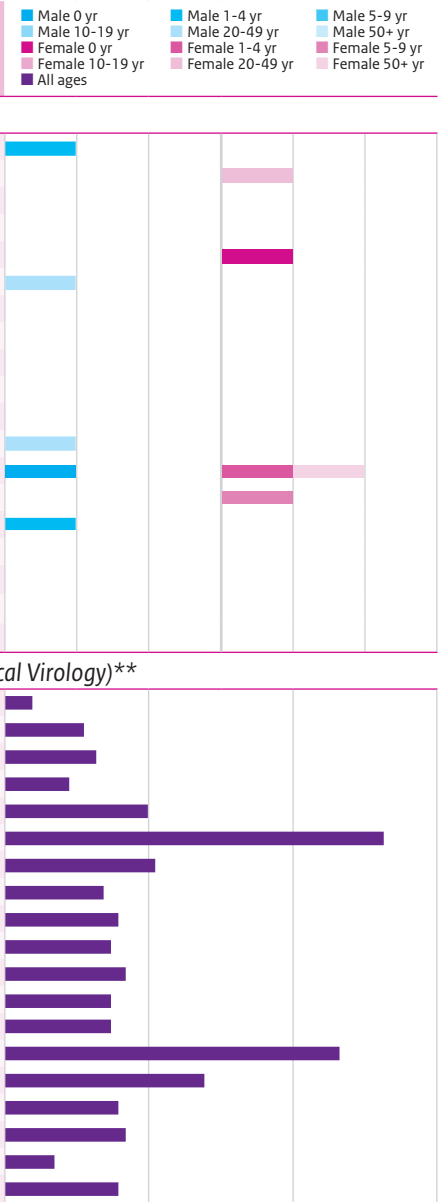


*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

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**
2015^	0	0	0	0	0	0	**0**
2016^	0	0	0	0	0	0	**0**
2017^	0	0	0	0	0	0	**0**
*Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)***							
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**
2018							**16**



*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.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases is not always actually 0, but can also be a few cases.

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

Tetanus — ID10: A33-35

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
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**
2018*	0	0	0	0	0	0	**0**
Notifications (source: Osiris)							
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**
2018	0	0	0	0	0	1	**1**

*Preliminary figures. From statistical year 2013 onwards, 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)								
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**	
2018*	0	0	0	0	0	1	**1**	

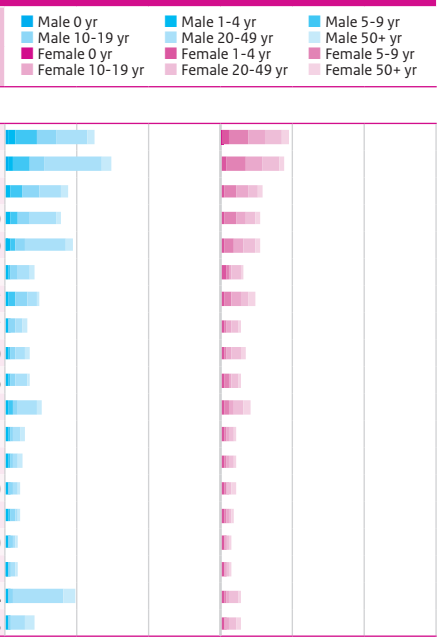
*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

Hepatitis A

ICD10: B15

Notifications (source: Osiris)*

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
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**
2018	0	9	8	27	89	55	**188**



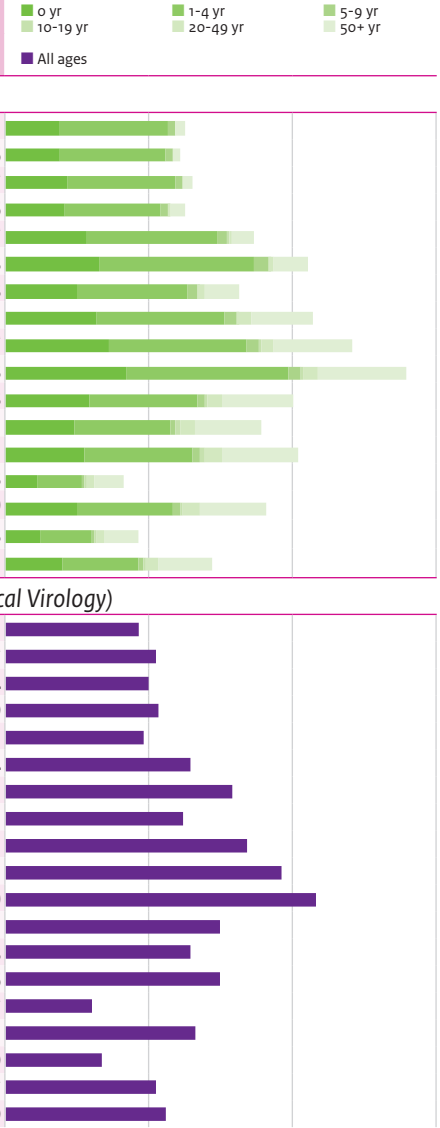
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)

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**
2018	**92**

*Age is unknown for 25 patients.

Rotavirus

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Hospitalisations (estimation; source: Prismant/DHD/CBS)*							
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**
2015^	1,496	2,020	150	72	335	1,416	**5,490**
2016^	768	1,037	77	37	172	727	**2,818**
2017^	1,184	1,599	119	57	265	1,121	**4,345**
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)							
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**
2018							**1,129**



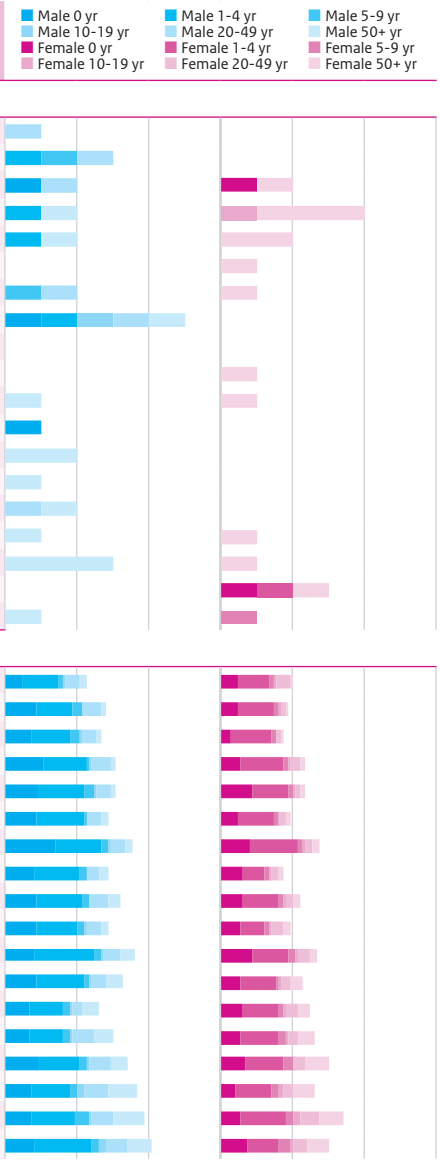
*Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ The estimates from 2015-2017 are based on the five previous years (2010-2014).

Varicella (chickenpox)

ICD9: 052
ICD10: B01

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
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**
2018*	0	0	1	0	0	1	**2**
*Hospitalisations** (source: Prismant/DHD/CBS)*							
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**
2015^	55	110	15	10	50	70	**315**
2016^	60	120	25	15	55	75	**355**
2017^	75	120	25	10	50	60	**345**



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

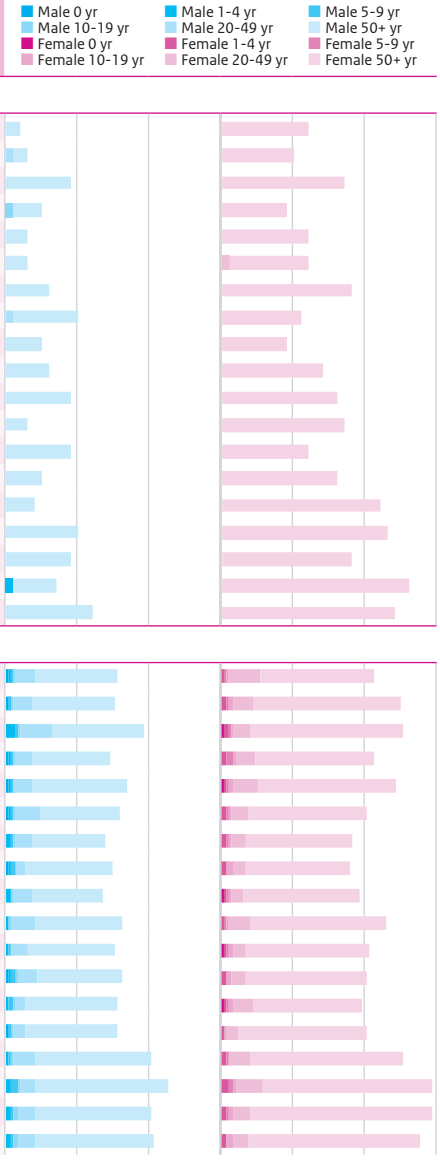
**Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases is not always actually 0, but can also be a few cases.

Herpes zoster (shingles)

ICD9: 053
ICD10: B02

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
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**
2018*	0	0	0	0	0	36	**36**
*Hospitalisations** (source: Prismant/DHD/CBS)*							
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**
2015^	0	10	10	15	60	415	**515**
2016^	0	10	10	10	45	415	**490**
2017^	0	15	5	20	45	405	**495**



*Preliminary figures. From statistical year 2013 onwards, the coding of 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.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases is not always actually 0, but can also be a few cases.

Appendix 3 Overview of vaccine changes in the NIP from 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.

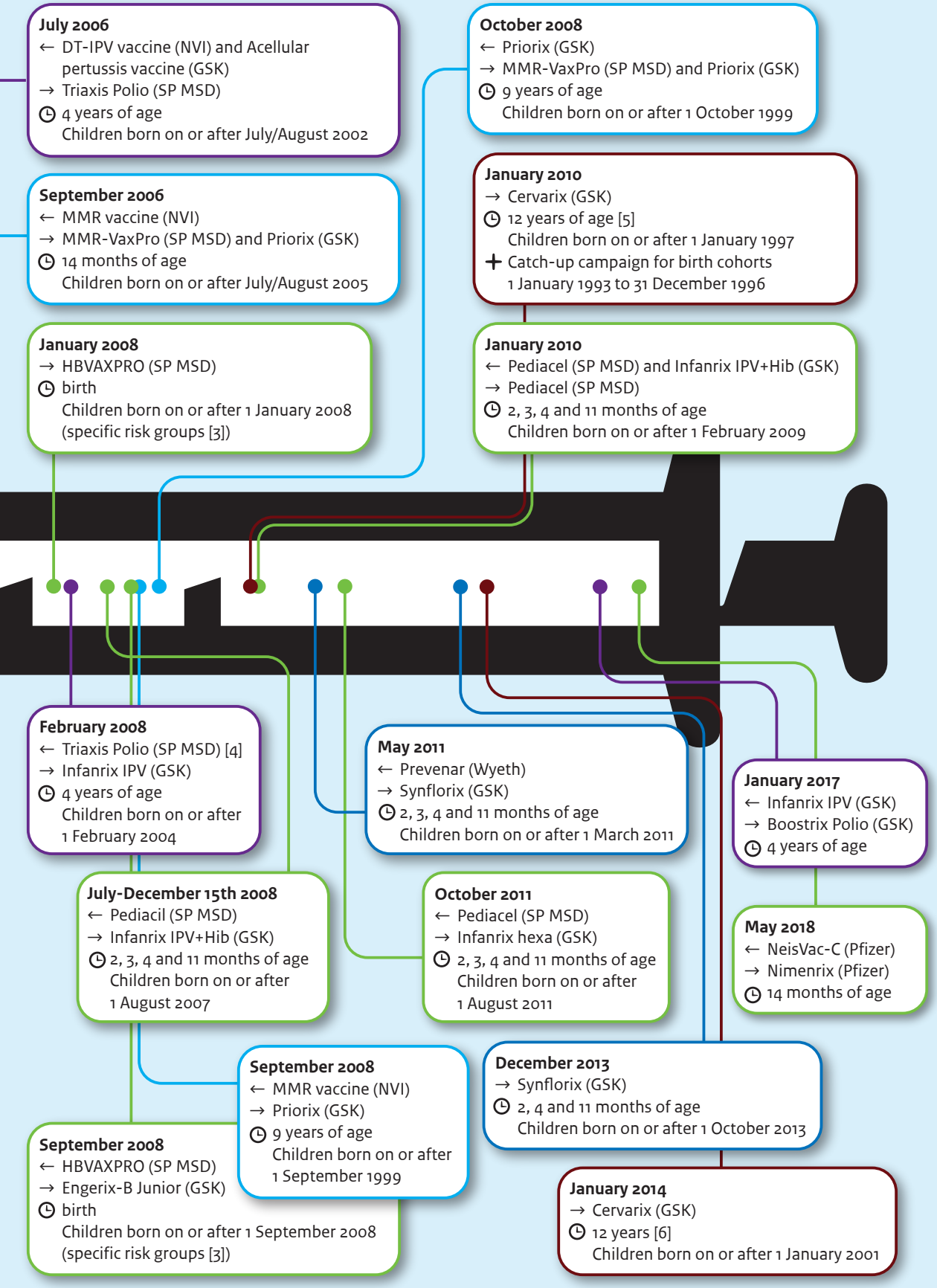
[2] Only for children whose mother tested positive for HBsAg.

[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
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
Vaxelis / MCM Vaccine B.V. EU/1/15/1079/007 Diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), inactivated poliomyelitis and *Haemophilus* type b vaccine (adsorbed) 0.5 ml	Diphtheria toxoid > 20 IE Tetanus toxoid > 40 IE Pertussis toxoid 20 mcg Filamentous haemagglutinin 20 mcg Fimbriae type 2 and 3 5 mcg Pertactin 3 mcg Inactivated type 1 poliovirus 40 DE Inactivated type 2 poliovirus 8 DE Inactivated type 3 poliovirus 32 DE *Haemophilus influenzae* type b polysaccharide 3 mcg Conjugated to meningococcal protein 50 mcg

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 aluminium hydroxide 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
Engerix-B / GSK RVG17316 Hepatitis B (rDNA) vaccine (adsorbed) 1 ml	Hepatitis B-virus surface antigen[1,2] 20 µg [1] Adsorbed on aluminium hydroxide, hydrated 0.5 mg AL^{3+} [2] Produced on yeast cells (Saccharomyces cerevisiae) with 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.*

Vaccine	Composition
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
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 (01/08/2018 to 31/08/2019)

Vaccination coverage

1. van Lier EA, Oomen PJ, Giesbers H, van Vliet JA, Drijfhout IH, Zonnenberg-Hoff IF, et al. Vaccinatiegraad en jaarverslag Rijksvaccinatieprogramma Nederland 2018. [Vaccination Coverage and Annual Report National Immunisation Programme Netherlands 2018]. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2019 (RIVM report 2019-0015).
2. Quee FA, Mollema L, van Vliet JA, de Melker HE, van Lier EA. Geen relatie tussen veranderingen in organisatorische aspecten met betrekking tot vaccineren binnen de jeugdgezondheidszorg en ontwikkeling in aantal gevaccineerden 2013-2017. [No link between organisational changes in youth healthcare services and the trend in vaccination levels from 2013 to 2017]. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu (RIVM); 2018 (RIVM report 2018-0111).
3. van Lier A, Mollema L, Quee FA, van Vliet JA, de Melker HE. Organisatorische veranderingen in de Nederlandse jeugdgezondheidszorg in relatie tot de ontwikkeling van de vaccinatiegraad in de periode 2013–2017. Tijdschr Jeugdgezondheidsz. 2019;51(3-4):89-93.
4. Nutma N, van Lier A, Drijfhout I, Oomen P, Goosen S, Slinger K, et al. Bereikt het Rijksvaccinatieprogramma asielzoekerskinderen? Een onderzoek naar de DKTP-vaccinatiegraad. Tijdschr Jeugdgezondheidsz. 2019;51(3-4):110-115.
5. Van Rossum C, Nutma N, Ruijter ELM, Ruijs WLM, Tostmann A. BMR-vaccinatiegraad van asielzoekerskinderen in GGD-regio Gelderland-Zuid. Tijdschr Jeugdgezondheidsz. 2019;51(3-4):116-121.

Acceptance of vaccination

1. Pot M, Ruiter RA, Paulussen TW, Heuvelink A, de Melker HE, van Vliet HJ, et al. Systematically developing a web-based tailored intervention promoting HPV-vaccination acceptability among mothers of invited girls using intervention mapping. 2018;6.
2. Pot M, Van Keulen H, Paulussen T, Otten W, Van Steenbergen J, Ruiter RJHPB. Mothers' Perceptions of their Daughters' Susceptibility to HPV-related Risk Factors: An Experimental Pretest Comparing Narrative and Statistical Risk Information. 2019;3(1).
3. Pot M, Paulussen, T. G. W. M., Ruiter, R. A. C., Mollema, L., Hofstra, M., Van Keulen, H. M. Dose-response relationship of a Web-based Tailored Intervention Promoting HPV Vaccination. 2019.
4. Mollema L, Antonise-Kamp L, van Vliet JA, de Melker HE. Organisatorische en communicatieve interventies die de opkomst voor HPV-vaccinatie kunnen verhogen. Tijdschr Jeugdgezondheidsz 2019;51: 101-105.

Burden of disease

1. de Gier B, Schimmer B, Mooij SH, Raven CFH, Leenstra T, Hahné SJM. State of Infectious Diseases in the Netherlands, 2018. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2019. RIVM report 2019-0069.
2. de Gier B, van Kassel MN, Sanders EAM, van de Beek D, Hahne SJM, van der Ende A, et al. Disease burden of neonatal invasive Group B Streptococcus infection in the Netherlands. PLoS One. 2019;14(5):e0216749.
3. van Lier A, de Gier B, McDonald SA, Mangen MJ, van Wijhe M, Sanders EAM, et al. Disease burden of varicella versus other vaccine-preventable diseases before introduction of vaccination into the national immunisation programme in the Netherlands. Euro Surveill. 2019;24(18):pii=1800363.
4. McDonald SA, Nijsten D, Bollaerts K, Bauwens J, Praet N, van der Sande M, et al. Methodology for computing the burden of disease of adverse events following immunization. Pharmacoepidemiol Drug Saf. 2018;27(7):724-30.

Adverse events

None

NIP-wide research topics

1. Hoes J, Knol MJ, Mollema L, Buisman A, de Melker HE, & van der Klis FRM. Comparison of antibody response between boys and girls after infant and childhood vaccinations in the Netherlands. Vaccine 2019.

Current NIP

Diphtheria

1. Vos RA, Mollema L, Kerkhof J, van den Kerkhof JH, Gerstenbluth I, Janga-Jansen AV, Stienstra Y, de Melker HE, van der Klis FR. Risk of Measles and Diphtheria Introduction and Transmission on Bonaire, Caribbean Netherlands, 2018. The American Journal of Tropical Medicine and Hygiene. 2019 May 20:tpmd180824.

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

None

Hepatitis B

1. Koopsen J, van Steenbergen JE, Richardus JH, Prins M, Op de Coul ELM, Croes EA, et al. Chronic hepatitis B and C infections in the Netherlands: estimated prevalence in risk groups and the general population. Epidemiol Infect. 2019;147:e147.
2. Suijkerbuijk AWM, van Hoek AJ, Koopsen J, de Man RA, Mangen MJ, de Melker HE, et al. Cost-effectiveness of screening for chronic hepatitis B and C among migrant populations in a low endemic country. PLoS One. 2018;13(11):e0207037.
3. Visser M, van der Ploeg CPB, Smit C, Hukkelhoven C, Abbink F, van Benthem BHB, et al. Evaluating progress towards triple elimination of mother-to-child transmission of HIV, syphilis and hepatitis B in the Netherlands. BMC Public Health. 2019;19(1):353.
4. Raven S, Urbanus A, de Gee A, Hoebe C, van Steenbergen J. Predictors of hepatitis B

vaccination completion among people who use drugs participating in a national program of targeted vaccination. Vaccine. 2018;36(35):5282-7.

Human papillomavirus (HPV) infection

1. Bogaards JA, van der Weele P, Woestenberg PJ, van Benthem BH, King AJ. Bivalent HPV Vaccine Effectiveness Correlates with Phylogenetic Distance from Hpv Vaccine Types 16 And 18. The Journal of Infectious Diseases. 2019.
2. Bogaards JA, Mooij SH, Xiridou M, van der Loeff MFS. Potential effectiveness of prophylactic HPV immunization for men who have sex with men in the Netherlands: A multi-model approach. PLoS medicine. 2019;16(3):e1002756.
3. Man I, Vänskä S, Lehtinen M, Bogaards JA. HPV type replacement: still too early to tell? EUROGIN 2018; FC 5-6 (conference abstract). 2018.
4. Man I, Auranen K, Wallinga J, Bogaards JA. Capturing multiple-type interactions into practical predictors of type replacement following human papillomavirus vaccination. Philosophical Transactions of the Royal Society B. 2019;374(1773):20180298.
5. Pasmans H, Schurink-Van't Klooster TM, Bogaard MJM, van Rooijen DM, de Melker HE, Welters MJP, van der Burg SH, van der Klis FRM, Buisman AM. Long-term HPV-specific immune response after one versus two and three doses of bivalent HPV vaccination in Dutch girls. Vaccine. 2019 Sep 28.
6. Schurink-van't Klooster, T. M., Donken, R., Schepp, R. M., van der Klis, F. R., & de Melker, H. E. (2018). Persistence of immune response following bivalent HPV vaccination: A follow-up study among girls routinely vaccinated with a two-dose schedule. Vaccine, 36(49), 7580-7587.
7. van der Weele, P., Breeuwsma, M., Donken, R., van Logchem, E., van Marm-Wattimena, N., et al. (2019). Effect of the bivalent HPV vaccine on viral load of vaccine and non-vaccine HPV types in incident clearing and persistent infections in young Dutch females. PloS one, 14(3), e0212927.
8. Woestenberg PJ, King AJ, Van Benthem BHB, Leussink S, Van der Sande MAB, Hoebe CJPA, et al. Bivalent Vaccine Effectiveness Against Anal Human Papillomavirus Positivity Among Female Sexually Transmitted Infection Clinic Visitors in the Netherlands. The Journal of Infectious Diseases. 2019.
9. Woestenberg PJ, Bogaards JA, King AJ, et al. Assessment of herd effects among women and heterosexual men after girls-only HPV16/18 vaccination in the Netherlands: A repeated cross-sectional study. Int J Cancer 2019; 144:2718-27.
10. Qendri, V., Schurink-Van't Klooster, T. M., Bogaards, J. A., & Berkhof, J. (2018). Ten years of HPV vaccination in the Netherlands: current evidence and future challenges in HPV-related disease prevention. Expert review of vaccines, 17(12), 1093-1104.
11. Qendri V, Bogaards JA, Berkhof J. Who Will Benefit From Expanding HPV Vaccination Programs to Boys? JNCI Cancer Spectrum. 2018;2(4):pky076.

Measles

1. Brinkman ID, de Wit J, Smits GP, Ten Hulscher HI, Jongerius MC, Abreu TC, et al. Early measles vaccination during an outbreak in The Netherlands: reduced short and long-term antibody responses in children vaccinated before 12 months of age. J Infect Dis. 2019.
2. Brinkman ID, de Wit J, Rots NY, van Baarle D, van Binnendijk RS. Vervroegde extra BMR-vaccinatie tijdens een mazelenuitbraak. Infectieziekten Bulletin. 2019;30(4).

Meningococcal disease

1. Brandwagt DAH, van der Ende A, Ruijs WLM, de Melker HE, Knol MJ. Evaluation of the surveillance system for invasive meningococcal disease (IMD) in the Netherlands, 2004-2016. BMC Infect Dis. 2019 Oct 17;19(1):860.
2. Krone M, Gray S, Abad R, Skoczyńska A, Stefanelli P, van der Ende A, et al. Increase of invasive meningococcal serogroup W disease in Europe, 2013 to 2017. Euro Surveill. 2019 Apr;24(14).
3. Loenenbach AD, van der Ende A, de Melker HE, Sanders EAM, Knol MJ. The Clinical Picture and Severity of Invasive Meningococcal Disease Serogroup W Compared With Other Serogroups in the Netherlands, 2015-2018. Clin Infect Dis. 2019 Sep 26.
4. Taha MK, Deghmane AE, Knol M, van der Ende A. Whole genome sequencing reveals Trans-European spread of an epidemic Neisseria meningitidis serogroup W clone. Clinical Microbiology and Infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2019;25(6):765-7.
5. van Ravenhorst MB, van der Klis FRM, van Rooijen DM, Sanders EAM, Berbers GAM. Use of saliva to monitor meningococcal vaccine responses: proposing a threshold in saliva as surrogate of protection. BMC Medical Research Methodology. 2019;19(1):1.

Mumps

1. Bodewes R, van Rooijen K, Cremer J, Veldhuijzen IK, van Binnendijk R. Optimizing molecular surveillance of mumps genotype G viruses. Infect Genet Evol. 2019;69:230-4.
2. Soetens L, Backer JA, Hahne S, van Binnendijk R, Gouma S, Wallinga J. Visual tools to assess the plausibility of algorithm-identified infectious disease clusters: an application to mumps data from the Netherlands dating from January 2009 to June 2016. Euro Surveill. 2019;24(12).
3. de Wit J, Emmelot ME, Poelen MC, Lanfermeijer J, Han WG, van Els CA, et al. The human CD4+ T cell response against mumps virus targets a broadly recognized nucleoprotein epitope. 2019;93(6):e01883-18.
4. Kaaijk P, Wijmenga-Monsuur AJ, van Houten MA, Veldhuijzen IK, Ten Hulscher HI, Kerkhof J, et al. A Third Dose of Measles-Mumps-Rubella Vaccine to Improve Immunity Against Mumps in Young Adults. The Journal of infectious diseases. 2019.
5. Kaaijk P. dWJ, Veldhuijzen I., van Binnendijk R.S, . Infectieziekten Bulletin, jaargang 30, themanummer Vaccinaties, nummer 4, april 2019. Bilthoven: Centrum Infectieziektenbestrijding, RIVM, 2019.

Pertussis

1. Barug D, Pronk I, van Houten MA, Versteegh FGA, Knol MJ, van de Kassteele J, et al. Maternal pertussis vaccination and its effects on the immune response of infants aged up to 12 months in the Netherlands: an open-label, parallel, randomised controlled trial. The Lancet Infectious Diseases. 2019;19(4):392-401.
2. Rots N. Kinkhoestvaccinatie van zwangeren en het vaccinatieschema voor hun baby's. Aanpassing gewenst? RIVM open repository: RIVM, 2018.
3. Hovingh ES. Unraveling the interactions between Bordetella pertussis and the innate immune system. Doctoral thesis. Utrecht University, 3 May 2018.
4. Hovingh ES, Kuipers B, Marinović AAB, Hamstra HJ, Hijdra D, Gras LM, et al. Detection of opsonizing antibodies directed against a recently circulating Bordetella pertussis strain in paired plasma samples from symptomatic and recovered pertussis patients. 2018;8(1):12039.
5. Hovingh ES, de Maat S, Cloherty AP, Johnson S, Pinelli E, Maas C, et al. Virulence associated gene 8 of Bordetella pertussis enhances contact system activity by inhibiting the regulatory function of complement regulator c1 inhibitor. 2018;9.
6. Hovingh ES, Mariman R, Solans L, Hijdra D, Hamstra H-J, Jongerius I, et al. Bordetella pertussis pertactin knock-out strains reveal immunomodulatory properties of this virulence factor. 2018;7(1):1-13.

Pneumococcal disease

1. Cremers AJH, Mobegi FM, van der Gaast-de Jongh C, van Weert M, van Opzeeland FJ, Vehkala M, et al. The Contribution of Genetic Variation of Streptococcus pneumoniae to the Clinical Manifestation of Invasive Pneumococcal Disease. Clin Infect Dis. 2019 Jan 1;68(1):61-69.
2. SpIDnet/I-MOVE+ Pneumo Group. Effect of childhood pneumococcal conjugate vaccination on invasive disease in older adults of 10 European countries: implications for adult vaccination. Thorax. 2019 May;74(5):473-482.
3. van Westen E, Knol MJ, Wijmenga-Monsuur AJ, Tcherniaeva I, Schouls LM, Sanders EAM, et al. Serotype-Specific IgG Antibody Waning after Pneumococcal Conjugate Primary Series Vaccinations with either the 10-Valent or the 13-Valent Vaccine. Vaccines. 2018;6(4).
4. Van de Garde MDBK, M.J. Rots, N.Y. Van Baarle, D. Van Els, C.A.C.M. Vaccines to protect older adults against pneumococcal disease. In: Weinberger E, editor. Vaccines For The Elderly: Present And Future 2019.
5. van de Garde MDB, van Westen E, Poelen MCM, Rots NY, van Els C. Prediction and Validation of Immunogenic Domains of Pneumococcal Proteins Recognized by Human CD4(+) T Cells. Infection and immunity. 2019;87(6).

Poliomyelitis

None

Rubella

None

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)
2. Gassowski M, Michaelis K, Wenzel JJ, Faber M, Figoni J, Mouna L, et al. Two concurrent outbreaks of hepatitis A highlight the risk of infection for non-immune travellers to Morocco, January to June 2018. Euro Surveill. 2018;23(27).
3. Ndumbi P, Freidl GS, Williams CJ, Mardh O, Varela C, Avellon A, et al. Hepatitis A outbreak disproportionately affecting men who have sex with men (MSM) in the European Union and European Economic Area, June 2016 to May 2017. Euro Surveill. 2018;23(33).

Respiratory syncytial virus

1. Vos LM, Teirlinck AC, Lozano JE, Vega T, Donker GA, Hoepelman AI, et al. Use of the moving epidemic method (MEM) to assess national surveillance data for respiratory syncytial virus (RSV) in the Netherlands, 2005 to 2017. Euro Surveill. 2019;24(20).
2. van Erp EA, Luytjes W, Ferwerda G, van Kasteren PB. Fc-Mediated Antibody Effector Functions During Respiratory Syncytial Virus Infection and Disease. Front Immunol. 2019;10:548.
3. van Erp EA, Feyaerts D, Duijst M, Mulder HL, Wicht O, Luytjes W, et al. Respiratory Syncytial Virus Infects Primary Neonatal and Adult Natural Killer Cells and Affects Their Antiviral Effector Function. J Infect Dis. 2019;219(5):723-33.

Rotavirus

1. van Dongen, J. and P. Bruijning-Verhagen, *Rotavirusinfecties en vaccinatie bij kinderen.* Nederlands tijdschrift voor medische microbiologie, 2018. 26(2): p. 76.

Varicella zoster virus (VZV) infection

1. van Lier A, de Gier B, McDonald SA, Mangen MJ, van Wijhe M, Sanders EAM, et al. Disease burden of varicella versus other vaccine-preventable diseases before introduction of vaccination into the national immunisation programme in the Netherlands. Euro Surveill. 2019;24(18).
2. 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 adjuvanted subunit and live-attenuated vaccines. BMC Med. 2018;16(1):228.

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, Department for Vaccine Supply and Prevention Programmes):
http://www.rivm.nl/RIVM/Organisatie/Centra/Dienst_Vaccinvoorziening_en_Preventieprogramma_s

Meldingsplicht infectieziekten (Duty to notify infectious diseases in the Netherlands):
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

Vaccines Today:
https://www.vaccinestoday.eu/about-us/who-we-are/

Other NIP-related RIVM reports

Immunisation coverage and annual report National Immunisation Programme in the Netherlands 2018:
https://www.rivm.nl/publicaties/vaccinatiegraad-en-jaarverslag-rijksvaccinatieprogramma-nederland-2018

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

Gezondheidsraad (Health Council of the Netherlands):
http://www.gezondheidsraad.nl/

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

Vaccine safety:
Netherlands Pharmacovigilance Centre Lareb:
http://www.lareb.nl/

College ter Beoordeling van Geneesmiddelen (CBG, Netherlands Medicines Evaluation Board):
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, Netherlands Institute for Health Services Research):
http://www.nivel.nl/

Nederlands Referentielaboratorium voor Bacteriële Meningitis (NRLBM, Netherlands Reference Laboratory for Bacterial Meningitis):
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, Netherlands Working Group Clinical Virology):
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/
https://www.cdc.gov/vaccines/growing/

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 Griekpreventie (SNPG, Foundation for the National Influenza Prevention Programme): *http://www.snpg.nl/*

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

Annual Report on Surveillance of influenza and other respiratory infections in the Netherlands:
https://www.rivm.nl/publicaties/annual-report-surveillance-of-influenza-and-other-respiratory-infections-winter

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

Annual Report on Surveillance of influenza and other respiratory infections in the Netherlands:
https://www.rivm.nl/publicaties/annual-report-surveillance-of-influenza-and-other-respiratory-infections-winter

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

Traveller vaccination
Landelijk Coördinatiecentrum Reizigersadvisering (National Coordination Centre for Information for Travellers):
https://www.lcr.nl/Index.htm

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