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

The National Immunisation Programme in the Netherlands

Surveillance and developments in 2019-2020

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Synopsis

The National Immunisation Programme in the Netherlands
Surveillance and developments in 2019-2020

In 2019 1,520,301 persons (children and pregnant women) were vaccinated under the National Immunisation Programme (NIP). These persons received 2,929,264 vaccinations in total. The national immunisation coverage has slightly increased for the first time in five years.

As in previous years, the number of notified cases in 2019 was low for *Haemophilus influenzae* type b (Hib, 39), diphtheria (0), tetanus (0), rubella (0), and polio (0). The number of measles cases in 2019 was relatively high with 84 reported cases. The number of mumps cases was low (131), but double than that of the previous year. The number of notifications of pertussis (...) and hepatitis B (1205) remained stable. The overall number of meningococcal disease (159) decreased after an increase from 2015 to 2018 (90 to 206).
In 2020 following implementation of Dutch COVID-19 response measures, the reported incidence of pertussis, invasive pneumococcal disease (IPD), invasive meningococcal disease (IMD), and mumps has decreased.

The estimated effectiveness of maternal pertussis vaccination in preventing pertussis in 0-3-month-olds was 73-90% in 2019, assuming a 20-40% vaccination coverage, and 93-97% in 2020, taking into account 50-70% coverage.
A study on the early effects of HPV vaccination on cervical lesions in opportunistic screening, found that fully vaccinated women (12-24 years of age) had a lower risk for an high-risk HPV infection (0.68; 95%CI 0.62-0.74), borderline (pre)neoplastic changes or worse (0.77; 0.73-0.82) and moderate to severe dysplasia or worse (0.45; 0.37-0.56) than unvaccinated women of the same age.

In 2020, PPV23 vaccination was to be offered to all 60-, 65-, 70- and 75-year-olds in the Netherlands. However, due to the COVID-19 pandemic, priority has been given to the oldest age groups, meaning that in Autumn 2020 all 73-79-year-olds will be offered PPV23 vaccination.
In 2020, the Health Council of the Netherlands issued a positive recommendation to add vaccination against varicella in the NIP in the Caribbean Netherlands and not in the European Netherlands. The council also recommends that residents of these islands who have not yet had an infection be offered a one-off vaccination against VZV.

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 2019-2020

In 2018 zijn 1.520.301 personen (kinderen en zwangeren) gevaccineerd via het
Rijksvaccinatieprogramma (RVP). In totaal ontvingen zij 2.929.264 vaccinaties. De landelijke vaccinatiegraad is voor het eerst sinds 5 jaar licht gestegen.

Net als in voorgaande jaren waren er in 2019 weinig meldingen van *Haemophilus influenzae* type b (Hib; 39), difterie (0), tetanus (0), rodehond (0) en polio (0). Het aantal meldingen van mazelen was met 84 relatief hoog. Het aantal meldingen van bof was laag (131), maar verdubbeld ten opzichte van het voorgaande jaar. Het aantal meldingen van kinkhoest (...) en hepatitis B (1205) bleef stabiel. Het totale aantal meldingen van meningokokkenziekte (159) daalde na een stijging van 2015 tot 2018 (90 tot 206).
In 2020 na de implementatie van de COVID-19 maatregelen is de gerapporteerde incidentie van kinkhoest, invasieve pneumokokkenziekte, invasieve meningokokkenziekte en bof gedaald.

De geschatte effectiviteit van maternale kinkhoestvaccinatie in het voorkomen van kinkhoest bij kinderen 0-3 maanden oud was 73-90%, uitgaande van een vaccinatiegraad van 20-40% in 2019 en 93-97% in 2020, rekening houdend met een vaccinatiegraad van 50-70%.
In een studie naar de vroege effecten van HPV vaccinatie op cervicale laesies in opportunistische screening, hadden volledig gevaccineerde vrouwen (12-24 jaar) een lager risico op een hoog-risico HPV infectie (0,68; 95%BI 0,62-0,74), borderline (pre)neoplastische veranderingen of erger (0,77; 0,73-0,82) en matig tot ernstige dysplasie of erger (0,45; 0,37-0,56) dan ongevaccineerde vrouwen van dezelfde leeftijd.

In 2020 zou PPV23-vaccinatie worden aangeboden aan alle 60-, 65-, 70- en 75-jarigen in Nederland. Vanwege de COVID-19-pandemie is echter prioriteit gegeven aan de oudste leeftijdsgroepen, wat betekent dat in het najaar van 2020 alle 73-79-jarigen PPV23-vaccinatie aangeboden zullen krijgen.
In 2020 heeft de Gezondheidsraad geadviseerd om vaccinatie tegen waterpokken in Caribisch Nederland wel toe te voegen aan het RVP en in Europees Nederland niet. De Gezondheidsraad adviseert ook om bewoners van deze eilanden die nog geen infectie hebben gehad een eenmalige vaccinatie tegen VZV 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)

Infographic

Preface

This report presents an overview of surveillance and developments 2019 and the first part of 2020 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, including COVID19 vaccines.

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 2019-2020. 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

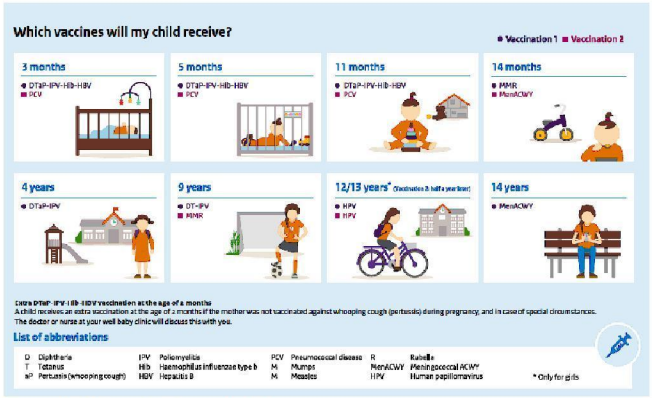


Figure 1 NIP vaccination schedule
Source:
http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals

Vaccination coverage

The national immunisation coverage has slightly increased for the first time in five years. In infants born in 2017, this applies in particular to the mumps, measles and rubella (MMR) vaccination. This rose by 0.7% to 93.6%. The national immunisation coverage for HPV vaccination (cervical cancer) for girls, born in 2005, has increased by 7.5% to 53%. The provisional national vaccination coverage for the meningococcal ACWY vaccination for adolescents born in 2001-2005 is high (86%). It is reassuring that the effect of the COVID-19 pandemic on participation in the first MMR vaccination seems limited, despite some vaccination delay.

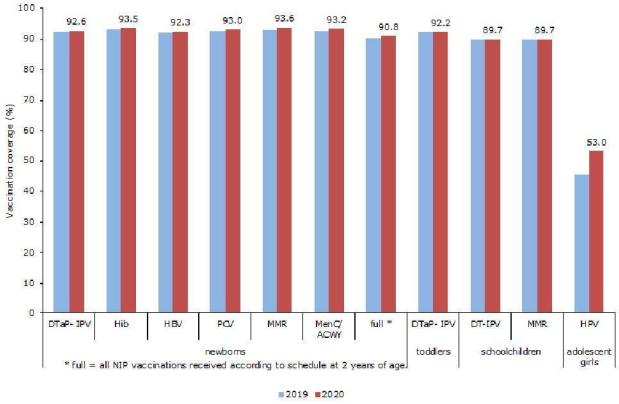


Figure 2 Vaccination coverage per vaccine for newborns, toddlers, schoolchildren and adolescent girls in 2019 and 2020
Source: Præventis

Acceptance of vaccination

Several quantitative and qualitative studies showed it is important to direct communication strategies and materials regarding vaccines at the target groups. For example, communication regarding the MenACWY vaccination should focus on both the teenagers and parents. Furthermore, including the relevant health care workers in this communication process is important. Research regarding the maternal pertussis vaccination (MPV) showed that the health care workers (i.e. midwives, gynaecologists) are the preferred source of information to women, regardless of them having heard or read about MPV already. Therefore, information should be tailored and consultation for target group could increase vaccine acceptance. These strategies should be implemented before mandates are enforced as the latter have shown to not necessarily be effective in increasing vaccine acceptance.

Burden of disease

For the year 2019, the estimated burden of disease caused by (partially) vaccine-preventable diseases, as expressed in Disability Adjusted Life Years (DALYs), was highest for HPV (19,400 DALYs (75% among women)), invasive pneumococcal disease (9,500 DALYs/year), pertussis (2,600 DALYs/year), rotavirus infection (1,100 DALYs/year), invasive *Haemophilus influenzae* disease (970 DALYs/year), and invasive meningococcal disease (890 DALYs/year). For most diseases, the estimated burden in 2019 was comparable to the estimated burden in 2018. The disease burden of invasive pneumococcal and meningococcal disease was lower in 2019, whereas the burden of HPV (for females), measles and pertussis was somewhat higher in 2019 than in 2018.

Adverse events

In 2019, Lareb received 2,009 notifications representing a total of 7,378 adverse events following immunisation (AEFI). Compared to 2018, the number of reports increased by 32%, while the number of reported AEFIs increased by 42%. The increase in number of reports is mainly due to the catch-up campaign of MenACWY vaccination in adolescents. The number of reported AEFIs per report remained stable (3.7).
No new signals of disturbing adverse events were found.

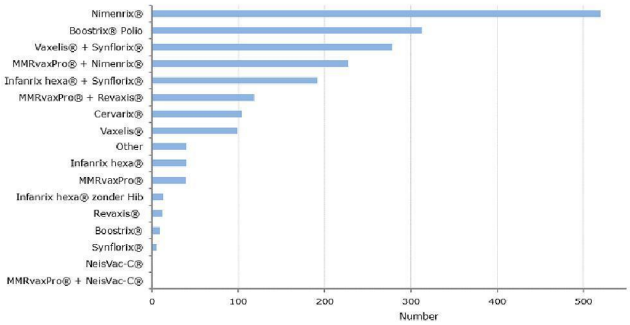


Figure 3 Number of reports of adverse events per suspected vaccine(s) in 2019
Source: Lareb

NIP-wide research topics

Following implementation of Dutch COVID-19 response measures, the reported incidence of pertussis, invasive pneumococcal disease (IPD), invasive meningococcal disease (IMD), and mumps has decreased.

Current NIP

Diphtheria

In 2019, one possible diphtheria case was reported with unknown vaccination history. Although clinical signs were very suspicious for diphtheria and patient received diphtheria antitoxin as treatment, no Corynebacterium was found. In 2020, until June 1st, no diphtheria cases were notified.
A European serosurveillance study showed that a substantial part of 40-60-year-olds had non-protective DT levels. Levels <0.01 IU/ml varied between 4% and 43%. For 0.1 IU/ml, these percentages varied from 23% up to around 80%. The percentage unprotected in the Netherlands was 12.8% (<0.01 IU/ml) and 57.5% (<0.1 IU/ml).

Haemophilus influenzae disease

In 2019, the number of cases of *Haemophilus influenzae* type b (Hib) disease was similar to 2018 (39 vs 43 cases). Up to May 2020, 16 Hib cases have been reported, somewhat more than in the same period in 2019 (n=10) but similar to 2018 (n=17). In 2019, the incidence of Hib disease was highest among children under 5 years old (2.0 per 100,000). After an increasing trend in incidence observed from 2011 to 2016, the incidence stabilized in the period 2017-2019. There were 19 Hib cases in vaccine-eligible children in 2019, of which nine were

sufficiently vaccinated, resulting in a Hib vaccine effectiveness estimate of 93%, similar to previous years. In 2019, a similar number of cases of non-typable Hi (NTHi) disease were reported as in 2018 (165 vs. 167), suggesting a stabilization of NTHi disease. No rise was observed in Hi due to other serotypes.

Hepatitis B

The incidence of acute hepatitis B reports (n=104) remained stable at 0.6 per 100,000 population in 2019. Sexual contact was the most frequently reported risk factor for acute HBV infection, but the route of transmission remained unknown for a third of cases. No cases of acute hepatitis B were reported among children born after the introduction of universal HBV vaccination in 2011. In 2019, genotype A continued to be the dominant genotype among acute HBV cases with 58% of 74 genotyped cases.
The number of newly diagnosed chronic HBV infections was 1,205 in 2019, corresponding to an incidence of 6.2 per 100,000.

Human papillomavirus (HPV) infection

The incidence of cervical cancer has been increasing in 2019 up to 9.90 per 100,000, while the number of deaths caused by cervical cancer has remained relatively stable. 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 nine years post-vaccination. This is also reflected in more clinically relevant findings: A study on the early effects of HPV vaccination on cervical lesions in opportunistic screening, found that fully vaccinated women (12-24 years of age) had a lower risk for hrHPV, ASC-US or worse and (H)SIL or worse. Moreover, using GP data from sentinel surveillance systems, it was shown that the bivalent HPV vaccine also provides partial protection against GW. Regarding seroprevalence data, type-specific HPV-seroprevalence increases were noted in unvaccinated women between 2006-07 and 2016-17 (Pienter studies). In men, overall HPV seroprevalence remained stable in the same period.

Measles

The number of measles cases in 2019 was relatively high with 84 notified cases. However, in the first six months of 2020 only 2 cases were reported. From June to August 2019 a local outbreak occurred in a low vaccination municipality with 32 reported cases, mainly among unvaccinated children. Genotype D8 was the only genotype detected. Preliminary analyses of the population-based serosurvey (PIENTER study) conducted in 2016/2017 indicate high overall seroprevalence of protective antibodies in the Dutch population of 97% for measles.

Meningococcal disease

In 2019, the overall incidence of meningococcal disease decreased after an increase from 2015 to 2018. In April to June 2020, the number of cases was 80% lower than in the same period in the last five years, which may be (partly) related to the COVID-19 measures that were in place during these months, including social distancing and school closures. The number of cases with meningococcal serogroup C disease is still very low, with six cases reported in 2019.

The vaccination uptake of the MenACWY vaccination campaign in 2018/2019 among 14-18 year olds was 84% and an additional 2% of the eligible population got vaccinated prior to the campaign. A lower uptake was observed when parents were born abroad, especially for parents born in Morocco or Turkey.
In 2019, the incidence of meningococcal serogroup W (MenW) disease decreased to 0.39 per 100,000 (n=62), after an increase in the number of cases from 2015 to 2018. In the first six months of 2020, only eight cases have been reported with no cases reported in April to June. The decrease of MenW in 2019 and the first months of 2020 was observed in vaccinated as well as unvaccinated age groups. Among children eligible for MenACWY vaccination at 14 months, there has been one vaccinated and one unvaccinated MenW case. Among adolescents eligible for MenACWY vaccination, there have been no MenW cases.
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 2019, 72 cases and five deaths of MenB disease were reported, which was similar to 2018 (74 cases and five deaths). The incidence of MenB disease was highest in children aged under 5 years, with 22 cases in 2018 (2.5 per 100,000). The number of cases of meningococcal disease caused by serogroup Y or other serogroups is low and stable.

Mumps

The incidence of mumps in 2019 was low (0.8 per 100,000 population; n=131) but doubled compared to the year before. The increase in cases continued in the first quarter of 2020 but stopped abruptly in the second quarter of 2020. Most of the mumps cases in the Netherlands were caused by mumps virus genotype G.

Pertussis

In 2019, the overall incidence rate (IR) of pertussis notifications was 36.8 per 100,000 compared with 28.4 per 100,000 in 2018. In 2020 up to April 1st, the IR was 16.6 per 100,000; this IR was probably affected by the control measures in view of the covid-19 pandemic.
In April and May 2020, vaccination coverage of the maternal pertussis vaccination was estimated to be about 70%. In 2019, estimates for the effectiveness of the maternal pertussis vaccination in preventing pertussis in 0-3-month-olds was 73%-90%s , assuming a 20%-40% vaccination coverage. For 2020, the VE amounted to 93%-97%, taking into account 50%-70% coverage.
The prevalence of prn-deficient strains in the Netherlands sharply increased in 2018-2020.

Pneumococcal disease

In April and May 2020, the number of IPD dropped by 80% compared with the 5-year average, most likely related to COVID-19 measures. This influenced the overall and age-specific incidence and time trends of IPD in 2019/2020. In epidemiological year 2019/2020 (June to May), 43 children <5 years of age with IPD were reported, of which only one case was caused by a serotype included in the 10-valent PCV.
In children <5 years of age, introduction of pneumococcal conjugate vaccination (PCV) in 2006 led to a large reduction of IPD. 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 covered by 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 89% (95%CI 72-96%) against vaccine type IPD. In 2020, PPV23 vaccination was to be offered to all 60-, 65-, 70- and 75-year-olds in the Netherlands. However, due to the COVID-19 pandemic, priority has been given to the oldest age groups, meaning that in Autumn 2020 all 73-79 year olds will be offered PPV23 vaccination.

Poliomyelitis

In 2019 and 2020 up to July 1st, no cases of poliomyelitis were reported in the Netherlands, including the Caribbean Netherlands.
In an historic announcement on World Polio Day (24 October 2019), an independent commission of experts concluded that wild poliovirus type 3 (WPV3) has been eradicated worldwide. Two of three wildtype polioviruses (i.e. WPV2 and WPV3) have been declared eradicated.
In 2019-2020, poliovirus remained endemic in three countries; Nigeria, Afghanistan and Pakistan. On 21 Augustus 2019 Nigeria, and thus the Afro region, was free of wildtype poliovirus for 3 consecutive years. The certification process to declare the 5th of 6 WHO regions wildtype polio free is in progress and will likely be finalized in 2020. Worldwide, the number of circulating vaccine derived poliovirus (cVDPV) was higher in 2019 (368) than in 2018 (105). To sustain a world free of all polioviruses, the Global Polio Eradication Initiative (GPEI) has released a Polio Endgame Strategy 2019-2023 in 2019.

Rubella

In 2019, no rubella cases were notified. Preliminary analyses of the population-based serosurvey (PIENTER study) conducted in 2016/2017 indicate high overall seroprevalence of protective antibodies in the Dutch population of 95% for rubella. The highest susceptibility in the PIENTER study was seen among children within the orthodox Protestant community, born after the last rubella epidemic in 2005, indicating an outbreak can be expected after introduction of rubella virus in this community.

Tetanus

In 2019, no cases of tetanus were notified. In 2020, up to June 1st, two cases were reported, one elderly women who was not eligible for routine vaccination and one unvaccinated 12-year-old.
In a European seroprevalence study among 40-59-year-olds, seroprotection levels for tetanus were sufficient with only very few sera lacking basic immunity. In the Dutch serum samples, based on Pienter 3 participants, only 0.3% and 5.2% had anti-tetanus antibody levels <0.01 IU/ml and <0.1 IU/ml, respectively.

The immunisation programme in the Caribbean Netherlands

In general, vaccination coverage in the Dutch overseas territories, including Caribbean Netherlands (i.e., Bonaire, St. Eustatius and Saba) is high. In 2019, no vaccine preventable diseases were reported on Bonaire and Saba.

Findings from the Health Study Caribbean Netherlands indicate that HPV seroprevalence was high among individuals aged ≥15 years (34%), with over half of them being seropositive for ≥2 high-risk HPV types. Seroprevalence was substantial higher in women (51%) than men (18%), predominantly peaking in women aged 20-59 years. These data corroborate the decision regarding introduction of a sex-neutral HPV-vaccination program and the relevance for considering a population-based cervical cancer screening program in Caribbean Netherlands.

Potential NIP target diseases

Hepatitis A

In 2019, the number of reported hepatitis A cases (n=164) slightly decreased compared to 2018 (n=188), but remains higher compared to 2011-2016 (80-125 cases). No cases related to the MSM outbreak in 2016-2018 were seen in 2019. However, two new strains caused outbreaks among men who have sex with men (MSM). About two-third of the reported cases in 2019 is 20 years or older. Forty-one per cent of the Dutch cases were reported to be travel-related, with Morocco reported most frequently.

Respiratory syncytial virus (RSV) infection

A total of 95 RS-viruses (6,4%) were detected in 1493 combined nose swabs and throat swabs of patients with an acute respiratory infection (ARI), collected by sentinel GPs in the 2019/2020 respiratory season, compared with 12% in 2018/2019, 6% in 2017/2018 and 12% in 2016/2017. Due to the Covid-19 pandemic, more samples were collected with different age distribution than previous seasons in weeks 10-20, possibly partly explaining the relatively low RSV percentage.

Rotavirus infection

In 2019, 1,056 detected cases of rotavirus were reported, which was slightly less compared to 2018 (n=1,140). In 2020, until May, almost half of the rotavirus cases have been observed compared to the same period in 2019 (2019 n=610; 2020 n=284). 43% (62/145) of the typed samples in 2019 corresponded to rotavirus serotype G9. The most prevalent genotypes were G9P8 (26%, 38/145) and G3P8 (28%, 40/145). The Ministry of Health, Welfare and Sport has decided in April 2020 to delay the implementation of rotavirus vaccination in the NIP.

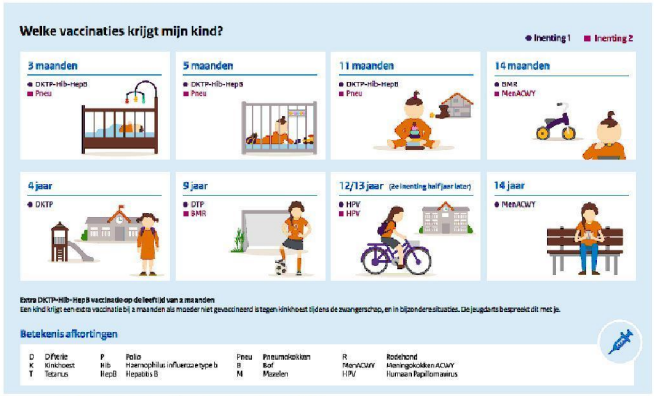
Varicella zoster virus (VZV) infection (varicella and herpes zoster)

The VZV epidemiology (incidence of GP consultations, hospitalisations and deaths) in the Netherlands is comparable to that of previous years; in 2018, GPs recorded about 45,000 varicella and 93,000 herpes zoster episodes (260 and 540 episodes per 100,000 population respectively).
In 2020, the Health Council of the Netherlands issued a positive recommendation to add vaccination against varicella in the NIP in the Caribbean Netherlands and not in the European Netherlands. The council also recommends that residents of these islands who have not yet had an infection be offered a one-off vaccination against VZV.
In July 2020, the revised Dutch guideline 'Varicella' has been published. It includes revised opinions on post-exposure prophylaxis (PEP) and a new module on varicella treatment.

Uitgebreide samenvatting

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

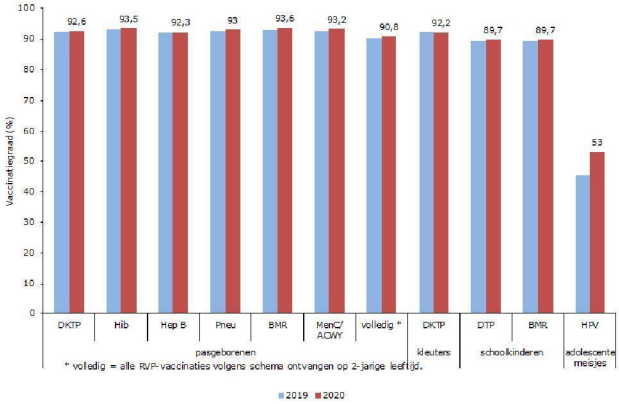
Huidig vaccinatieschema



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

Vaccinatiegraad

De landelijke vaccinatiegraad is voor het eerst sinds 5 jaar licht gestegen. Bij zuigelingen, geboren in 2017, geldt dit in het bijzonder voor de vaccinatie tegen bof, mazelen en rodehond (BMR). Deze is met 0,7% gestegen tot 93,6%. De landelijke vaccinatiegraad voor de HPV-vaccinatie (baarmoederhalskanker) voor meisjes, geboren in 2005, is met 7,5% toegenomen tot 53%. De voorlopige landelijke vaccinatiegraad voor de meningokokken ACWY-vaccinatie voor adolescenten geboren in 2001-2005 is hoog (86%).
Het is geruststellend dat het effect van de COVID-19-pandemie op deelname aan de eerste BMR-vaccinatie, ondanks enige vertraging in vaccinatie, beperkt lijkt.



Figuur 2 Vaccinatiegraad per vaccin voor pasgeborenen, kleuters, schoolkinderen en adolescente meisjes in verslagjaar 2019 en 2020
Bron: Præventis

Acceptatie van vaccinatie

Verschillende kwantitatieve en kwalitatieve studies hebben aangetoond dat het belangrijk is om de communicatie en communicatiestrategieën rondom vaccinaties toe te spitsen op de doelgroep(en). Zo blijkt dat de communicatie rondom MenACWY zich zou moeten richten op ouders, maar ook tieners. Verder is het betrekken van relevante zorgprofessionals in het communicatieproces essentieel. Onderzoek naar de maternale kinkhoestvaccinatie (MKV) heeft aangetoond dat vrouwen de informatie het liefst krijgen via hun zorgprofessional (verloskundige, gynaecoloog). Dit geldt ook voor vrouwen die nog niet hadden gehoord of gelezen over MKV. Informatie die op maat gemaakt is zodat het zo goed mogelijk aansluit bij de doelgroep(en) en tijdens spreekuren wordt gegeven kan de acceptatie van vaccinaties verhogen. Deze ontwikkelingen zouden eerst doorgevoerd moeten worden, voordat wordt overgegaan op meer verplichtende maatregelen omtrent vaccineren, omdat onderzoek heeft aangetoond dat verplichtende maatregelen de acceptatie van vaccinaties niet per se verhoogd.

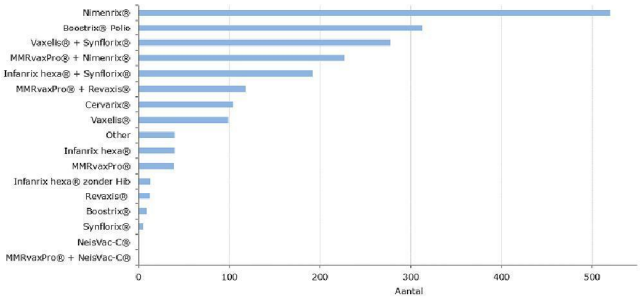
Ziektelast

De geschatte ziektelast veroorzaakt door ziekten die (deels) door vaccinatie te voorkomen zijn, uitgedrukt in Disability Adjusted Life Years (DALYs), was in 2019 het hoogst voor HPV (19.400 DALYs (75% voor vrouwen)), invasieve pneumokokkenziekte (9.500 DALYs per jaar), kinkhoest (2.600 DALYs per jaar), rotavirusinfectie (1.100 DALYs per jaar), invasieve ziekte veroorzaakt door *Haemophilus influenzae* (970 DALYs per jaar) en invasieve meningokokkenziekte (890 DALYs per jaar). Voor de meeste ziekten was de geschatte ziektelast in 2019 vergelijkbaar met de geschatte ziektelast in 2018. De ziektelast van invasieve pneumokokken- en meningokokkenziekte was in 2019 lager,

terwijl de ziektelast van HPV (voor vrouwen), mazelen en kinkhoest in 2019 iets hoger was dan in 2018.

Bijwerkingen

In 2019 ontving Bijwerkingencentrum Lareb 2.009 meldingen van in totaal 7.378 mogelijke bijwerkingen van vaccins. In vergelijking met 2018 is het aantal meldingen gestegen met 32%. Dit wordt hoofdzakelijk veroorzaakt door de inhaalcampagne van de meningokokken ACWY vaccinatie bij 14-18 jarigen. Het aantal geregistreerde mogelijke bijwerkingen na vaccinatie per melding was overeenkomstig met voorgaande jaren (3,7).
Er werden geen nieuwe signalen van verontrustende bijwerkingen gevonden.



Figuur 3 Aantal meldingen van mogelijke bijwerkingen per vaccin(s) in 2019
Bron: Lareb

RVP-brede onderzoeksthema's

Na de implementatie van de COVID-19 maatregelen is de gerapporteerde incidentie van kinkhoest, invasieve pneumokokkenziekte, invasieve meningokokkenziekte en bof gedaald.

Huidig RVP

Difterie
In 2019 werd één mogelijk geval van difterie gemeld met een onbekende vaccinatiegeschiedenis. Hoewel de klinische symptomen zeer verdacht waren voor difterie en de patiënt difterie-antitoxine kreeg als behandeling, werd er geen Corynebacterium gevonden. In 2020 werden tot 1 juni geen gevallen van difterie gemeld.
Een Europese serosurveillance-studie toonde aan dat een substantieel deel van de 40-60-jarigen niet-beschermende DT-spiegels had. Niveaus <0,01 IU/ml varieerden tussen de 4% en 43%. Voor 0,1 IU/ml varieerden deze percentages van 23% tot circa 80%. Het percentage onbeschermden in Nederland was 12,8% (<0,01 IE/ml) en 57,5% (<0,1 IE/ml).

Haemophilus influenzae-ziekte
In 2019 was het aantal meldingen van *Haemophilus influenzae* type b (Hib) ziekte vergelijkbaar met 2018 (39 versus 43 gevallen). Tot mei 2020 zijn 16 Hib-gevallen gerapporteerd, iets meer dan in dezelfde

periode in 2019 (n=10) maar vergelijkbaar met 2018 (n=17). In 2019 was de incidentie van de Hib het hoogst bij kinderen jonger dan 5 jaar (2,0 per 100.000). Na een stijgende trend in incidentie waargenomen tussen 2011 en 2016, stabiliseerde de incidentie zich in de periode 2017-2019. Er waren 19 Hib-gevallen bij kinderen die in aanmerking kwamen voor vaccinatie in 2019, waarvan er negen voldoende waren gevaccineerd, wat resulteerde in een schatting van de effectiviteit van het Hib-vaccin van 93%, vergelijkbaar met voorgaande jaren. In 2019 werd een vergelijkbaar aantal gevallen van niet-typeerbare Hi (NTHi) ziekte gemeld als in 2018 (165 vs. 167), wat duidt op een stabilisatie van de NTHi-ziekte. Er werd geen stijging waargenomen in Hi ziekte door andere serotypen.

Hepatitis B
De incidentie van acute hepatitis B-meldingen (n=104) bleef stabiel in 2019 op 0,6 per 100.000 inwoners. Seksueel contact was de meest gemelde risicofactor voor een acute HBV-infectie, maar de transmissieroute bleef onbekend in een derde van de gevallen. Er werden geen gevallen gemeld van acute hepatitis B onder kinderen geboren na de introductie van universele HBV vaccinatie in 2011. In 2019 bleef genotype A het dominante genotype onder acute HBV-gevallen met 58% van de 74 getypeerde gevallen.
Het aantal nieuw gediagnosticeerde chronische HBV-infecties was 1.205 in 2019, dat overeenkomt met een incidentie van 6,2 per 100.000 inwoners.

Human papillomavirus (HPV)-infectie
De incidentie van baarmoederhalskanker is in 2019 toegenomen tot 9,90 per 100.000 terwijl het aantal doden veroorzaakt door baarmoederhalskanker stabiel is gebleven. De incidentie van andere HPV-gerelateerde kankers was tevens stabiel. In een prospectieve cohortstudie (HAVANA) werd een hoge vaccineffectiviteit (VE) gevonden tegen aanhoudende vaginale infecties tot in ieder geval 9 jaar na de vaccinatie. Deze bevindingen worden bevestigd in meer klinische setting: In een studie naar de vroege effecten van HPV vaccinatie op cervicale laesies in opportunistische screening, hadden volledig gevaccineerde vrouwen (12-24 jaar) een lager risico op hrHPV, ASC-US of erger en (H)SIL of erger. Daarnaast werd in surveillance huisartsendata aangetoond dat het bivalente vaccin ook deels bescherming biedt tegen (ano)genitale wratten. Met betrekking tot seroprevalentie bleek dat type specifieke HPV-seroprevalentie verhogingen werden waargenomen bij niet-gevaccineerde vrouwen tussen 2006-07 en 2016-17 (Pienter-onderzoeken). Bij mannen bleef de algehele HPV-seroprevalentie in dezelfde periode stabiel.

Mazelen
Het aantal mazelen gevallen was relatief hoog in 2019 met 84 meldingen. In de eerste zes maanden van 2020 zijn echter slechts 2 gevallen gemeld. Van juni tot augustus 2019 was er een lokale uitbraak in een gemeente met een lage vaccinatiegraad waarbij 32 gevallen gemeld werden, voornamelijk onder ongevaccineerde kinderen. Genotypen B3 en D8 werden gedetecteerd. De voorlopige analyse van de nationale serosurvey (PIENTER studie) uitgevoerd in 2016/2017 laat

een hoge seroprevalentie zien van 97% beschermende antistoffen tegen mazelen in de algemene Nederlandse bevolking.

Meningokokkenziekte
In 2019 daalde de totale incidentie van meningokokkenziekte na een stijging van 2015 tot 2018. In april tot juni 2020 was het aantal gevallen 80% lager dan in dezelfde periode in de afgelopen vijf jaar, wat mogelijk (deels) gerelateerd met de COVID-19 maatregelen die in deze maanden van kracht waren, waaronder sociale distantiëring en sluiting van scholen. Het aantal gevallen met meningokokken serogroep C is nog steeds erg laag, met zes gerapporteerde gevallen in 2019.
De vaccinatiegraad van de MenACWY-vaccinatiecampagne in 2018/2019 onder 14-18-jarigen was 84% en een extra 2% van de voor vaccinatie in aanmerking komende bevolking werd voorafgaand aan de campagne gevaccineerd. Een lagere vaccinatiegraad werd waargenomen wanneer ouders in het buitenland werden geboren, vooral voor ouders geboren in Marokko of Turkije.
In 2019 daalde de incidentie van meningokokken serogroep W (MenW) ziekte tot 0,39 per 100.000 (n=62), na een toename van het aantal gevallen van 2015 tot 2018. In de eerste zes maanden van 2020 zijn er slechts acht gevallen gemeld zonder meldingen in april tot juni. De afname van MenW in 2019 en de eerste maanden van 2020 werd zowel bij gevaccineerde als bij niet-gevaccineerde leeftijdsgroepen waargenomen. Onder de kinderen die op 14 maanden in aanmerking komen voor MenACWY-vaccinatie, was één gevaccineerd en één niet-gevaccineerd MenW-geval. Onder adolescenten die in aanmerking kwamen voor MenACWY-vaccinatie, waren er geen gevallen van MenW.
De incidentie van meningokokken serogroep B (MenB) ziekte neemt gestaag af sinds eind jaren negentig en is gestabiliseerd op een incidentie van 0,5 per 100.000 sinds 2011. In 2019 werden 72 ziektegevallen en vijf sterfgevallen door MenB gemeld, vergelijkbaar met 2018 (74 gevallen en vijf doden). De incidentie van MenB was het hoogst bij kinderen onder de 5 jaar, met 22 gevallen in 2018 (2,5 per 100.000).
Het aantal gevallen van meningokokkenziekte veroorzaakt door serogroep Y of andere serogroepen is laag en stabiel.

Bof
De incidentie van bof was laag in 2019 (0,8 per 100.000; n=131) maar het dubbele van het voorgaande jaar. De stijging in het aantal meldingen zette door in het eerste kwartaal van 2020, maar stopte abrupt in het tweede kawrtaal van 2020. De meeste bofgevallen in Nederland werden veroorzaakt door het bofvirus genotype G.

Kinkhoest
In 2019 bedroeg de totale incidentie van kinkhoestmeldingen 36,8 per 100.000 vergeleken met 28,4 per 100.000 in 2018. In 2020 tot 1 april bedroeg de incidentie 16,6 per 100.000; deze incidentie werd waarschijnlijk beïnvloed door de controlemaatregelen door de COVID-19 pandemie.
In april en mei 2020 werd de vaccinatiegraad van de maternale kinkhoestvaccinatie geschat op ongeveer 70%. In 2019 waren de schattingen voor de effectiviteit van de maternale kinkhoestvaccinatie in het voorkomen van kinkhoest bij kinderen 0-3 maanden oud 73-90%,

uitgaande van een vaccinatiegraad van 20-40%. Voor 2020 bedroeg de vaccineffectiviteit 93-97%, rekening houdend met een dekking van 50-70%.
De prevalentie van prn-deficiënte stammen in Nederland is in 2018-2020 sterk gestegen.

Pneumokokkenziekte
In april en mei 2020 is het aantal invasieve pneumokokken ziekten (IPD) met 80% gedaald ten opzichte van het vijfjarig gemiddelde, hoogstwaarschijnlijk is dit gerelateerd aan COVID-19 maatregelen. Dit had invloed op de algemene en leeftijdsspecifieke incidentie en tijdstrends van IPD in 2019/2020. In het epidemiologische jaar 2019/2020 (juni tot mei) werden 43 kinderen <5 jaar met IPD gerapporteerd, waarvan slechts één geval werd veroorzaakt door een serotype opgenomen in de 10-valent PCV.
Bij kinderen <5 jaar heeft de introductie van pneumokokkenconjugaat-vaccinatie (PCV) in 2006 geleid tot een grote afname van IPD. Sinds 2013/2014 is de IPD-incidentie bij kinderen <5 jaar echter licht gestegen als gevolg van een langzame toename van IPD veroorzaakt door serotypen die niet worden gedekt door het 10-valente PCV. In andere leeftijdsgroepen werden vergelijkbare trends waargenomen met een zeer lage incidentie van IPD veroorzaakt door vaccinserotypen en een toenemende incidentie van IPD als gevolg van niet-vaccinserotypen, waardoor de algehele impact van PCV-implementatie in gevaar kwam. Vaccineffectiviteit (VE) van ten minste twee doses PCV10 was 89% (95% BI 72-96%) tegen vaccintype IPD. In 2020 zou PPV23-vaccinatie worden aangeboden aan alle 60-, 65-, 70- en 75-jarigen in Nederland. Vanwege de COVID-19-pandemie is echter prioriteit gegeven aan de oudste leeftijdsgroepen, wat betekent dat in het najaar van 2020 alle 73-79-jarigen PPV23-vaccinatie aangeboden zullen krijgen.

Polio
In 2019 en 2020 tot 1 juli zijn er geen gevallen van poliomyelitis gemeld in Nederland, ook niet in Caribisch Nederland.
In een historische aankondiging op Wereld Polio Dag (24 oktober 2019) concludeerde een onafhankelijke commissie van experts dat wild poliovirus type 3 (WPV3) wereldwijd is uitgeroeid. Twee van de drie wildtype poliovirussen (WPV2 en WPV3) zijn uitgeroeid verklaard.
In 2019-2020 bleef poliovirus endemisch in drie landen; Nigeria, Afghanistan en Pakistan. Op 21 augustus 2019 was Nigeria, en dus de Afro-regio, 3 opeenvolgende jaren vrij van wildtype poliovirus. Het certificeringsproces om de 5e van de 6 WHO-regio's wildtype polio-vrij te verklaren is aan de gang en zal waarschijnlijk in 2020 worden afgerond. Wereldwijd was het aantal circulating vaccine derived poliovirus (cVDPV) in 2019 hoger (368) dan in 2018 (105). Om een wereld vrij van alle poliovirussen in stand te houden, heeft het Global Polio Eradication Initiative (GPEI) in 2019 een Polio Endgame Strategy 2019-2023 uitgebracht.

Rodehond
In 2019 werden geen gevallen van rodehond gemeld. De voorlopige analyse van de nationale serosurvey (PIENTER studie) uitgevoerd in 2016/2017 laat een hoge seroprevalentie zien van 95% beschermende antistoffen tegen rubella in de algemene Nederlandse bevolking. In de

PIENTER studie werd de hoogste vatbaarheid gezien onder kinderen in de orthodox Protestante gemeenschap geboren na de laatste rubella epidemie in 2005. Dit geeft aan dat introductie van rubellavirus in deze gemeenschap kan leiden tot een uitbraak.

Tetanus
In 2019 zijn er geen gevallen van tetanus gemeld. In 2020 werden tot 1 juni twee gevallen gemeld, een oudere vrouw die niet in aanmerking kwam voor routinevaccinatie en een niet-gevaccineerde 12-jarige.
In een Europese seroprevalentiestudie onder 40-59-jarigen waren de seroprotectieniveaus voor tetanus voldoende, waarbij slechts zeer weinig sera geen basisimmuniteit hadden. In de Nederlandse serummonsters, gebaseerd op Pienter3-deelnemers, had slechts 0,3% en 5,2% anti-tetanus-antilichaamspiegels van respectievelijk <0,01 IE/ml en <0,1 IE/ml.

Het vaccinatieprogramma in Caribisch Nederland
Over het algemeen is de vaccinatiegraad in de Nederlandse overzeese gebiedsdelen, inclusief Caribisch Nederland (Bonaire, Sint Eustatius en Saba) hoog. In 2019 zijn op Bonaire en Saba geen ziekten gemeld die door vaccinatie te voorkomen zijn.
Bevindingen uit de Gezondheidsstudie Caribisch Nederland laten zien dat HPV-seroprevalentie hoog was bij personen van ≥15 jaar (34%), waarvan meer dan de helft seropositief was voor ≥2 hoog-risico HPV-typen. De seroprevalentie was aanzienlijk hoger bij vrouwen (51%) dan bij mannen (18%), voornamelijk bij vrouwen van 20-59 jaar. Deze gegevens bevestigen het besluit tot invoering van een gender-neutraal HPV-vaccinatieprogramma en de relevantie voor het overwegen van een bevolkingsonderzoek naar baarmoederhalskanker in Caribisch Nederland.

Potentiële RVP-kandidaten
Hepatitis A
Er werden in 2019 164 hepatitis A gevallen gerapporteerd. Dit is een kleine daling ten opzichte van 2018 (n=188), maar nog steeds hoger dan in de jaren 2011-2016 (80-125 gevallen). Er waren geen nieuwe gevallen gerelateerd aan de MSM-uitbraak van 2016-2018. Wel veroorzaakten twee nieuwe stammen uitbraken onder mannen die seks hebben met mannen (MSM). Ongeveer tweederde van de gemelde gevallen in 2019 betrof een volwassene (≥20 jaar). 41% Van de Nederlandse gevallen was reis-gerelateerd, voornamelijk met reizen naar Marokko.

Respiratoir syncytieel virus (RSV)-infectie
In totaal werden 95 RS-virussen (6,4%) gedetecteerd in 1493 gecombineerde neus- en keeluitstrijkjes van patiënten met een acute luchtweginfectie (ARI), verzameld door peilstationartsen in het respiratoire seizoen 2019/2020, vergeleken met 12% in 2018/2019, 6% in 2017/2018 en 12% in 2016/2017. Vanwege de COVID-19-pandemie werden in de weken 10-20 meer monsters afgenomen met een andere leeftijdsverdeling dan voorgaande seizoenen, wat mogelijk deels het relatief lage percentage RSV verklaart.

Rotavirusinfectie
Er werden in 2019 1,056 rotavirus gevallen gerapporteerd, wat iets minder is dan het aantal gevallen in 2018 (n=1,140). Tot mei 2020 zijn bijna de helft van de rotavirus gevallen geobserveerd, in vergelijking met dezelfde periode in 2019 (2019: n=610; 2020: n=284). 43% van alle getypeerde monsters in 2019 betrof rotavirus serotype G9 (62/145). De meeste geïdentificeerde genotypen waren G9P8 (26%, 38/145) en G3P8 (28%, 40/145). Het ministerie van Volksgezondheid, Welzijn en Sport heeft in april 2020 besloten de implementatie van vaccinatie tegen het rotavirus in het Rijksvaccinatieprogramma uit te stellen.

Varicella zoster virus (VZV)-infectie (waterpokken en gordelroos)
De epidemiologie van VZV (huisartsenbezoeken, ziekenhuisopnames en sterfgevallen) is vergelijkbaar met voorgaande jaren: in 2018 werden door huisartsen ongeveer 45.000 waterpokken- en 93.000 gordelroosepisodes gerapporteerd (respectievelijk 260 en 540 episodes per 100.000 inwoners).
In 2020 heeft de Gezondheidsraad geadviseerd om vaccinatie tegen waterpokken in Caribisch Nederland wel toe te voegen aan het RVP en in Europees Nederland niet. De Gezondheidsraad adviseert ook om bewoners van deze eilanden die nog geen infectie hebben gehad een eenmalige vaccinatie tegen VZV aan te bieden.
In juli 2020 is de herziene Nederlandse richtlijn 'Varicella' gepubliceerd. Deze bevat herziene adviezen over profylaxe na blootstelling (PEP) en een nieuwe module over de behandeling van waterpokken.

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.

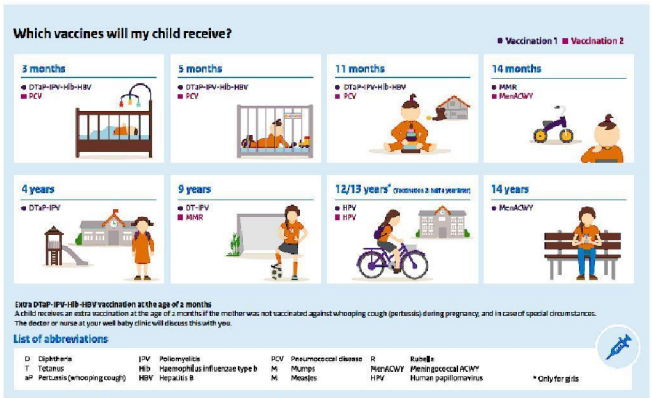


Figure 1.1 NIP vaccination schedule
Source: http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals

1.1.1 *Changes in the vaccination schedule*

The implementation of maternal pertussis vaccination in the context of the NIP started in December 2019.

1.1.2 *Number of vaccinated children*

In 2019, 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 2019, 1,520,301 persons (children and pregnant women) were immunised under the Dutch NIP. Together they received a total of 2,929,264 vaccine doses.

1.2 New recommendations and decisions

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

In 2020, PPV23 vaccination was to be offered to all 60-, 65-, 70- and 75-year-olds in the Netherlands. However, due to the COVID-19 pandemic,

priority has been given to the oldest age groups, meaning that in Autumn 2020 all 73-79 year olds will be offered PPV23 vaccination.

1.2.2 *New recommendations from the Health Council of the Netherlands*

In 2020, the Health Council of the Netherlands issued a positive recommendation to add vaccination against varicella in the NIP in the Caribbean Netherlands and not in the European Netherlands. The council also recommends that residents of these islands who have not yet had an infection be offered a one-off vaccination against VZV.

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 [1-4].
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 [5].
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, 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.

1.5 Literature

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*RIVM publication

2. Vaccination coverage

E.A. van Lier

2.1 Key points

- The national immunisation coverage has slightly increased for the first time in five years.
- In infants born in 2017, this applies in particular to the mumps, measles and rubella (MMR) vaccination. This rose by 0.7% to 93.6%.
- The national immunisation coverage for HPV vaccination (cervical cancer) for girls, born in 2005, has increased by 7.5% to 53%.
- The provisional national vaccination coverage for the meningococcal ACWY vaccination for adolescents born in 2001-2005 is high (86%).
- It is reassuring that the effect of the COVID-19 pandemic on participation in the first MMR vaccination seems limited, despite some vaccination delay.

2.2 Tables and figures

Table 2.1 Vaccination coverage (%) per vaccine for age cohorts of newborns, toddlers, schoolchildren and adolescent girls in 2006–2020 [1]

Reporting year	Newborns*							
	Cohort	DTaP-IPV	Hib	HBV[a]	PCV **	MMR	MenC/ ACWY	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
2020	**2017**	**92.6**	**93.5**	**92.3**	**93.0**	**93.6**	**93.2**	**90.8**

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
2020	**2014**	**89.9**	**2.4**	**92.2**	**2009**	**89.7**	**89.7**	**2005**	**53.0**

* 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

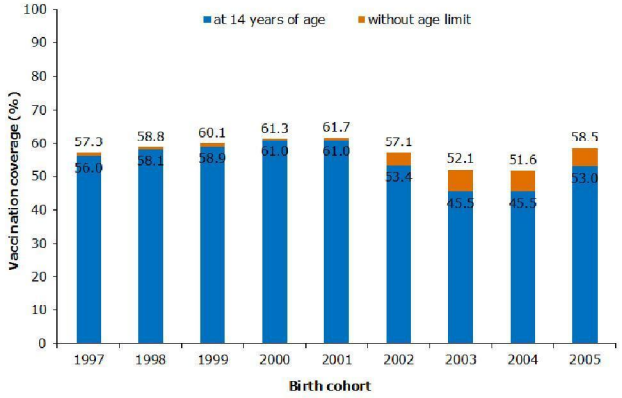

Figure 2.1 HPV vaccination coverage determined at 14 years of age and without age limit, by birth cohort [1]

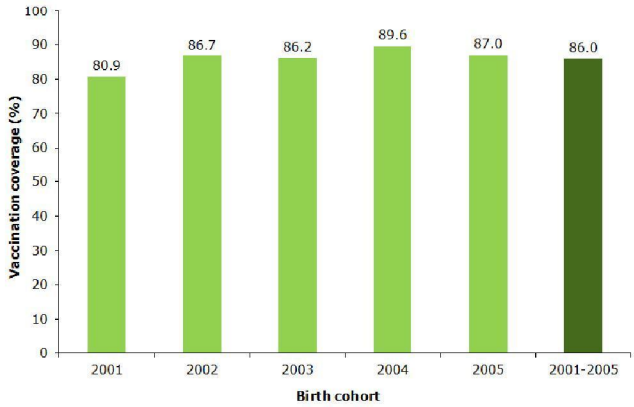

Figure 2.2 Vaccination coverage for meningococcal ACWY vaccination for adolescents, by birth cohort (preliminary figures) [1]

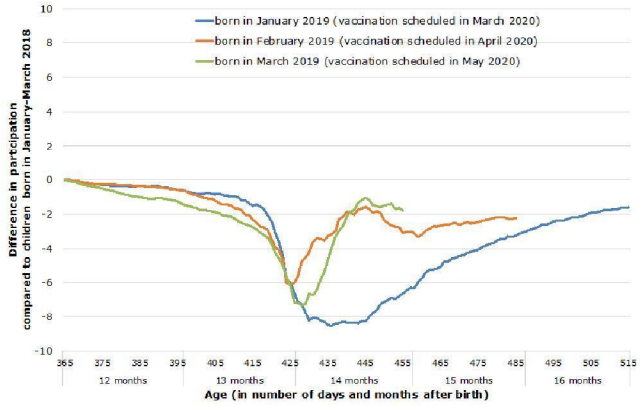

Figure 2.3 Difference in participation in the first measles-mumps-rubella vaccination (MMR1) of children born in January-March 2019 compared to children born in January-March 2018
Note: Children are scheduled to be vaccinated at the age of 14 months. Children born in January, February and March 2019 were scheduled to be vaccinated in March, April and May 2020, respectively. A difference of -8 at 436 days after birth means that the percentage vaccinated for children born in January 2019 (scheduled to be vaccinated in March 2020) at that age was 48% instead of 56% for children born in January 2018.

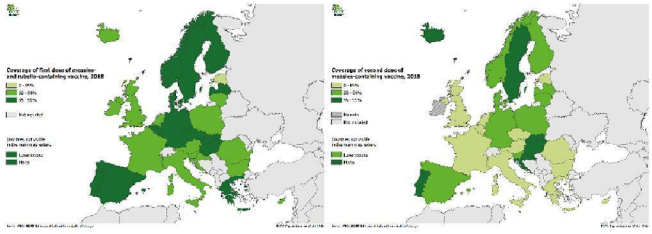

Figure 2.4 Vaccination coverage for first (left) dose of measles and rubella-containing vaccine and second (right) dose of measles-containing vaccine, EU/EEA and the UK, 2018 [2]

2.3 Vaccination coverage

2.3.1 *National developments*

The national vaccination coverage for most vaccinations has increased slightly compared to last year (Table 2.1). In infants born in 2017, the increase for the MMR vaccination is greatest (+0.7% to 93.6%). The increase (+7.5%) in the national HPV vaccination coverage to 53% for girls born in 2005 is striking. The provisional vaccination coverage among girls who are one year younger is currently already at 59% and

is expected to increase even further. In addition, the results for HPV also showed a catch-up effect (vaccination after the age of 14 years), especially for the birth cohorts 2002 to 2005 (Figure 2.1). Furthermore, the national participation among adolescents born in the period 2001-2005 in the MenACWY vaccination is high (preliminary vaccination coverage 86% (Figure 2.2); some of these adolescents will receive another reminder).
In toddlers born in 2014 we see a slight decrease (-0.3% to 92.2%) in the national vaccination coverage for DTaP-IPV (Table 2.1). However, it concerns children who were less often vaccinated against DTaP-IPV as an infant (-0.7%: 93.5% for children born in 2014 versus 94.2% for children born in 2013). Some of the children therefore caught up with the vaccination at a later time, as the difference at the age of five years has narrowed [1].

So for the first time in five years, there has been a slight increase in the vaccination coverage. The extra media attention for the subject of vaccination and the various national and regional initiatives aimed at increasing the vaccination coverage seem to be bearing fruit. The threat of the meningococcal W outbreak may also have played a role. Hopefully, this improvement in vaccination coverage will continue in the future because the vaccination coverage has not yet returned to its old level of about six years ago [1].

2.3.2 *Future challenges*

2.3.2.1 Effect of COVID-19 pandemic

The vaccination coverage in Table 2.1 concerns children who have been vaccinated before 2020. It is currently unclear to what extent the COVID-19 pandemic will have an effect on vaccination coverage in the coming years. The extent of the effect of this pandemic on the vaccination coverage depends on the duration of the crisis and whether missed vaccinations are still made up (in time). Preliminary data (situation at 16 july 2020) showed that the participation of children in the first MMR vaccination (given around 14 months of age) who are scheduled to be vaccinated in March-May 2020 was delayed. However, as a result of catch-up vaccination, participation now is only ~2% lower compared to the previous year (Figure 2.3). More children are expected to be vaccinated in the coming months. The final vaccination coverage is not determined until the age of 2. For children born in 2019 and 2020, this will be done in the years 2022 and 2023. At the moment it is still too early to be able to say anything about participation in older age groups.

2.3.2.2 Differentiation NIP and informed consent

Insight into vaccination data at individual level, through the national registration system Præventis, has so far made it possible to identify small changes in vaccination coverage in a timely manner. For example, the signal of the declining vaccination coverage, which has now turned, could be taken up professionally by many, but especially by the NIP implementers. However, from 2020 the complexity of the vaccination schedule, and with it the vaccination coverage calculation, will increase. In order to continue to detect changes in the vaccination coverage in time, additional information is needed, such as whether a child was premature at birth and whether his/her mother was vaccinated against whooping cough during pregnancy. At the moment not all necessary additional information is available. It is also not known which part of the population will consent to the exchange of vaccination data between JGZ and RIVM in the future by means of the informed consent that will be implemented [1].

2.3.3 *International developments*

Over 100,000 measles cases were reported in the WHO European Region for the period January to October 2019. This number exceeds the 2018 total and is over three times the total reported in 2017. These figures highlight that although measles vaccination coverage has improved overall in the region, many people remain susceptible [3].
Only five countries (Hungary, Malta, 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 of measles- and rubella-containing vaccine in 2018 (see Figure 2.4) [2].
In 2018, vaccination coverage for the first dose rose to above 95% in Finland and Malta and dropped to below 95% in Austria compared to 2017. For the second dose, vaccination coverage rose to above 95% in Malta compared to 2017 [2].

2.3.3.1 Effect of COVID-19 pandemic

In other countries such as England and the United States, the first MMR and DTaP-IPV vaccinations also showed a decrease when the COVID-19 pandemic started. However, this decrease was larger than in the Netherlands. Abroad, too, after an initial sharp decline, the proportion of children vaccinated increased again after some time [4-6].

2.4 Literature

2.1.1 *References*

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*RIVM publication

2.1.2 *Other recent RIVM publications*

1.* de Oliveira Bressane Lima P, van Lier A, de Melker H, Ferreira JA, van Vliet H, Knol MJ. MenACWY vaccination campaign for adolescents in the Netherlands: Uptake and its determinants. Vaccine. 2020;38(34):5516-24.

3. Acceptance of vaccination

K. van Zoonen, T. M. Schurink-van t Klooster, C. Oostdijk, M. de Vries, M. D. Wennekes, H. de Melker, E. Rikkengaa, L. Visser, L. Mollema

3.1 Key points

- A questionnaire study showed that health care workers are the most important source of information for women regarding the MPV.
- Quantitative and qualitative studies showed communication regarding the MenACWY vaccination should emphasize the safety and effectiveness of vaccines, and should focus on both teenagers and parents.
- Tailored information and/or consultation especially for target groups that are associated with lower HPV-vaccination might help to increase the HPV-vaccination uptake.
- International studies showed mandates alone are not necessarily effective in increasing vaccine acceptance and therefore uptake.

3.2 Monitoring acceptance NIP

Acceptance of the NIP and specific vaccines as well as intention to get vaccinated is monitored by the RIVM. In this chapter several studies are discussed regarding some relevant developments in the NIP. For example, the maternal pertussis vaccination was included in the Dutch NIP. With the inclusion of the maternal pertussis vaccination, the current NIP now includes vaccinations from pre-birth up to 14 years of age. However, prior to its inclusion the vaccine was available to pregnant women as an 'additional' vaccine (i.e. available at own request and costs). Furthermore, the Ministry of Health, Welfare and Sport decided to adopt the Health Council's advice on the HPV vaccination [1]. Other developments were the MenACWY vaccination "catch-up campaign" for adolescents and the inclusion of the MenACWY vaccination to the NIP for infants and adolescents. There was also an advice about the pneumococcal vaccination for the elderly [2]. Furthermore, several studies have focused on strategies and interventions that might increase vaccine uptake (such as mandates).

3.3 Pregnancy (pre-birth)

3.3.1 *Maternal pertussis vaccination*

Before the maternal pertussis vaccination (MPV) was included in the NIP (end of 2019), the RIVM conducted a study among pregnant and nonpregnant women focusing on their awareness, information seeking behaviour and vaccination uptake. The study aimed to examine whether (extra) communication efforts regarding MPV lead to awareness among women. The women that were not pregnant at the time of the study, had to have a child under the age of two years. This would mean the women had been pregnant after the decision of the minister in 2017 to include the vaccine in the NIP, but before it was decided when the vaccination would be included in the NIP. During this period, the communication about the vaccination was increased (e.g. information flyers and factsheets for health care professionals (HCPs) as well as the public were made available). A total of 942 women were included of

which 358 women were pregnant (38%). The study showed that most women are aware of MPV and engaged with MPV (i.e. felt MPV was an important topic to them). Women in both groups reported their HCW as preferred source of information. In addition, the public health institute (PHI) website was mentioned as a source for (additional)information. This study was conducted before the implementation of MPV and showed a relatively high percentage of women who reported to have been vaccinated during their (last) pregnancy (43% of all pregnant and 38% of nonpregnant women). This indicates that the (extra) communication strategies about the vaccination might have been effective in increasing awareness and possibly uptake. This is most likely due to educating the relevant HCP on maternal pertussis vaccination as well as including them in providing the information to the target group (e.g. pregnant women). However, these percentages might also be relatively high because women were relatively motivated by the topic and we used self-reported measures.

3.4 Adolescents

3.4.1 *MenACWY*

To prepare for and to assess the implementation (of the MenACWY vaccination) and the catch-up campaign in late-2018 and its expansion in 2019, several studies at the RIVM were conducted; one focused on knowledge, beliefs and intention to vaccinate in adolescents and parents before the vaccination, and another focused on the decision-making process and actual vaccination behaviour [3].
With the aim to study what teenagers and their parents knew and believed about meningococcal disease, the MenACWY vaccination, and vaccinations in general, and which aspects of knowledge and specific beliefs predict MenACWY vaccination intentions of teenagers and their parents. Adolescents who were invited for the menACWY catch-up vaccination campaign and their parents were surveyed about their knowledge and beliefs about meningococcal disease, the menACWY vaccination, vaccinations in general, and menACWY vaccination intentions. Random forest analysis was applied to study predictions of vaccination intentions by these knowledge and beliefs. The survey response rate was 52.8% among teenagers (N=1,603) and 57.1% among parents (N=1,784). Adolescents and their parents were generally inclined to receive the menACWY vaccination. Both groups seemed aware of the severity and contagiousness of invasive meningococcal disease (IMD), but there were also knowledge gaps and misbeliefs. For example, we found a relatively strong agreement in our study population for the misbelief that vaccines annually cause the death of several children in the Netherlands. Knowledge and beliefs concerning the effectiveness of, need for, and safety of vaccines in general were the strongest predictors of menACWY vaccination intentions in parents, surpassing knowledge and beliefs about meningococcal disease and the menACWY vaccination. For adolescents, the will of their parent(s) was the strongest predictor of their own vaccination intention. For future communication accompanying vaccination campaigns combatting outbreaks, the authors recommend concentrating on filling knowledge gaps and addressing specific misbeliefs about the effectiveness and safety of vaccines. In addition, to optimize vaccination uptake during future outbreaks, the authors recommend emphasizing the effectiveness

and safety of vaccines to parents and continuing to focus communication efforts on both parents and adolescents [3].

The study regarding the decision-making process about the menACWY vaccine consisted of a qualitative and a quantitative part. The aim was to gain insight into how households/parents and adolescents make a decision regarding the menACWY vaccination. It looked at what factors influenced both parents and adolescents during their decision-making and what they needed to make such a decision. It targeted parent and adolescent dyads who were invited to the catch-up campaign of late 2018 and early 2019. The qualitative part consisted of 20 households, totalling 38 interviews (20 parents/18 adolescents). Of these, seven households (7 parents/5 adolescents) had decided not to get the menACWY vaccine. The quantitative part consisted of 1,093 parents and 878 adolescents who completed an online questionnaire. This resulted in 506 parent/adolescent dyads, with others being the sole participant from their household. Among the parents 87% reported their child getting the menACWY vaccine. Among the adolescents 92% reported getting the menACWY vaccine.

The deliberations people made when deciding about the menACWY vaccination were partly related to ideas specifically concerning meningococcal disease and the vaccination itself and partly influenced by previously held convictions about vaccinations.

During interviews parents of vaccinated adolescents mentioned that the disease "seems scary", that infection "can happen just by getting sneezed on" and that the possible rapid progression of the disease contributed to making a swift decision. Simultaneously they indicated that "vaccinating is just a given" and is something they "do not really think about". The questionnaire showed that among the households where the adolescent had been fully vaccinated according the National Immunisation Programme (NIP), the majority (93%) also chose to get the menACWY vaccine.

Of the parents who got their child vaccinated 83% indicated not thinking about their decision very long. The opposite was the case among parents whose adolescent did not get the menACWY vaccine. A majority of these parents (61%) indicated that they had elaborately deliberated about their decision and thus had not made a swift decision.

Most parents discussed the choice for or against the menACWY vaccine with their child. But the preference of the parent(s) was often determinative for the final decision within a household. However, the adolescents experienced this differently. Of the adolescents, 23% indicated they themselves had made the final call on whether or not to get the menACWY vaccine. This contrasts with only 5% of parents who indicated their child made the final call for themselves

Parents and adolescents from the same households – either vaccinated or not - had corresponding attitudes, made similar deliberations and had similar reasons for their decisions. The most mentioned reasons not to get vaccinated were the low risk of getting meningococcal disease and the idea that the vaccine is not good for your health. Adolescents also specifically mentioned a dislike or even fear of getting vaccinated.

Insight into the decision-making processes of both parents and adolescents provides an understanding of the intra-household dynamics that occur with vaccinations targeting adolescents. This in turn offers insight into different decision-making processes for those accepting and those rejecting this vaccination and provides opportunities to target

communications more effectively aimed at those most influential in the different ways of decision-making.

3.4.2 *HPV*

The vaccination coverage of HPV for adolescent girls is still relatively low in the Netherlands. A literature study was conducted to examine the strategies that were put in place in order to increase vaccine uptake in Europe [4]. The age at which the vaccine is administered varies widely across Europe, between 9 and 15 years old. Furthermore, the setting in which the vaccine is administered varies. Ireland and Denmark have developed tailored information/education for HCP as well as the public. They used social media extensively and set up an alliance with several stakeholders. Literature shows that using reminders (before the vaccine is administered), a no-show policy, tailored information/education, reporting the vaccine coverage to HCP and lowering barriers to receiving the vaccine will lead to an increase in vaccine-uptake between 10 to 20%. It remains highly important that HCP promote the vaccine and help counter misinformation and/or misperception about the HPV-vaccine [4].
The Dutch Health Council advised to also vaccinate boys and lower the vaccination age to the year in which children turn 10 years old and the exploration of the possibilities of offering the HPV vaccine up to the age of 26. To gain insight in the number of vaccines needed, the RIVM conducted a study which aimed to explore the intention to vaccinate among (parents of) boys and the younger and older target groups. For this study unvaccinated girls and boys 9 to 17 years of age were randomly selected from the national vaccination registry (Praeventis). In addition, young women and men 18 to 26 years of age were randomly selected from the population registry. Selected persons (or the parents in case the adolescent was younger than 16 years of age) received an invitation letter with a link to a webpage with some basic information on HPV-vaccination and a link to an online questionnaire containing questions about the intention and attitude to HPV-vaccination. Participants that were already vaccinated (301 of the 1091), didn't have to answer the questions on intention and attitude.
The participation was 9.6% (n=191) and 9.2% (n=367) for the (parents of) younger (9-17 yr) and older (18-26 yr) girls respectively. For (parents of) younger and older boys the participation was 6.5% (n=392) and 7.1% (n=141), respectively. Results showed that the intention and attitude among girls varied between 15-69%, which was the highest among the youngest girls 9-10 years of age and very low among girls 18-21 and 22-26 years of age. The intention and attitude was higher among boys than among girls, i.e. varying between 56-79%, and the highest among the youngest boys 9-10 years of age and oldest boys 22-26 years of age. The most important reasons to vaccinate were protection against cancer, expected regret in case of no vaccination and getting cancer, and because it's offered by the government. The most important reasons not to vaccinate were adverse events and the uncertainty of long-term effects.

3.4.3 *HPV for boys*

In order to provide input on the parents' views and awareness of the HPV vaccination for boys, the RIVM recently conducted a qualitative study that focused on their beliefs, associations about HPV vaccination

for their nine/ten year old son and their intention to vaccinate their son against HPV. Parents were interviewed over the phone and asked about their associations with HPV and the HPV vaccine as well as with vaccinations in general. Furthermore, questions regarding their attitude towards and intention to vaccinate their son against HPV. They were also asked about their views on several visual presentations about HPV vaccination. This information will be used in the upcoming public campaign when HPV vaccination for boys will be implemented.
In another sub-study, visuals on HPV vaccination are developed to make parents aware of the link between HPV infection/ vaccination and cancer, and to enhance their understanding of the risk of HPV infection and effectiveness of the vaccination. The visuals will be tested on relevance and usability in focus group interviews with parents. The effectiveness and underlying mechanisms of the visuals will be assessed in a quantitative study. Results of these studies are expected in the fall of 2020.

3.5 Adults

3.5.1 *Pneumococcal vaccination for the elderly*

In the fall of 2020 elderly people (e.g. 73 up to 79 years old) will be invited to get vaccinated against pneumococcal disease [2]. The state secretary follows the advice given by the Dutch Health Council in April 2020 stating that people who are 73 years or older are at higher risk for a more severe course of pneumococcal disease compared to those aged 60 to 72 years.
An international project where the National Institute for Public Health and the Environment participates in, VITAL, is currently being conducted. One focus is to work out ways to educate and train HCPs involved in caring for older adults regarding the importance of vaccinations for this age group.
An important step is to understand perceptions of older adults regarding elderly vaccination. This has been studied by conducting focus groups among older adults in Hungary, France, Italy and The Netherlands. Preliminary results indicated a strong need among older adults for more information on vaccines. They would like to receive information on: side-effects, effectiveness of the vaccine, susceptibility for the disease and safety of the vaccine when combined with pre-existing health problems. The GP, and to a lesser extent specialists and pharmacists, play an important role in the information provision on vaccines to older adults.
Another step is to understand the perspectives of HCPs on vaccines for older adults. As well as what information needs HCPs may have regarding these vaccines. In 2020/2021 individual interviews with HCPs will be conducted. The results of these interviews will be validated quantitatively by means of a questionnaire. Furthermore, two literature reviews are being conducted which focus on identifying educational interventions for HCPs that have proven to be effective, as well as barriers HCPs experience in the communication with older adults on vaccines.

3.6 Communication

From December 2019 onward the maternal pertussis vaccination is included in the NIP. It is called the "22-weeks shot" and can be administered to pregnant women who are at least 22 weeks pregnant. Specific communication materials were developed, such as an

information pamphlet (available in several languages), posters and a website (www.22wekenprik.nl). The materials were pretested in the target group.
Through the website women can make an appointment at the youth health care centre in their neighbourhood. Prior to the introduction of MPV a public campaign was started. This campaign consisted of advertorials/articles in magazines (online and print), banners, a video and materials to include in free giftboxes for pregnant women. During this first period of administrating MPV the women all received a pink band-aid.
The HPV vaccine for boys will also be included in the NIP in the near future. This means that all 9 year old children, boys and girls, will receive an invitation to get the HPV vaccination. It will be possible to receive this vaccination for free to all Dutch citizens until they are 26 years old.
A public campaign will be part of this introduction to make the Dutch citizens aware. The most important target groups will be parents of 9/10 years old children, adolescents up to the age of 16 years, young adults up to the age of 18 years and HCPs. The goal is to make a clear and tailored message to all target groups to maximize acceptance of, and intention to get vaccinated with, the HPV vaccination. We will use behavioural knowledge to put emphasis on the prevention of cancer (not just HPV) and use narrative stories of (ex)patients and their family members/friends. There will also be a focus on the (media)dynamics regarding HPV and many external parties have indicated to be willing to partner up.

3.7 Strategies and interventions to increase vaccine uptake

Several strategies to increase vaccine uptake in a sustainable way are discussed during several conferences and reported on in articles [5, 6]. For example, it was identified that parents should seek information about vaccines from scientific and medical sources that are not based on misinformation and unproven alternatives. Also, health care professionals (HCP) need tools and training in order for them to effectively engage in vaccination acceptance conversations with parents. The role of mandates is also discussed, but as other research in countries with mandates has shown this should be complemented with other strategies, such as more time for HCP to the practice of vaccination counselling [5, 7].
In the Netherlands, Nivel and Amsterdam UMC conducted a study examining the effectiveness of measures to increase vaccine uptake and examined the suitability of these measures to the Dutch context [8]. They identified four types of measures; 1) mandates; 2) financial incentives; 3) measures that support the logistics of vaccination; 4) communication and promoting knowledge. They conclude that the first two types are less suitable to the Dutch context. However, it is likely that only a small portion of people that refuse vaccinations will be motivated to receive vaccinations by removing practical barriers (such as forgetting an appointment). When people refuse vaccinations based on religion it would be more suitable to focus on communication and knowledge enhancement. Furthermore, they conclude that it is necessary to get a better view of people who do not vaccinate and for what reasons in order to make sure the most adequate measure is chosen to increase the vaccine uptake. Also, the measures discussed in

the study, which were introduced in other countries, lack evaluation which makes it difficult to interpret the effectiveness.

3.8 International literature and studies

3.8.1 *MenACWY*

In the UK several studies were conducted to examine the influence of school characteristics and/or area-level factors on the uptake of MenACWY vaccine [9, 10].
One study focused on five school characteristics; overall effectiveness score (i.e. Ofsted; Effectiveness scores at schools last inspection); type of school; number of pupils eligible for the MenACWY vaccine within the school; percentage of total school population eligible for free school meals; percentage of total school population with English as a second language [10]. This study showed that the overall uptake rate was 80.7% and uptake rates were associated with all five school characteristics considered. Effectiveness scores for schools (i.e. quality of education, behaviour and attitudes, personal development of pupils, leadership and test results) had the largest association with vaccine uptake, with poorer schools having lower uptake. Another study showed that independent, special schools and pupil referral units had lower vaccination coverage compared to state-funded secondary schools [9].
In the US menACWY vaccination is a recommended routine vaccination administered at ages 11-12 years with a booster at age 16 years [11, 13]. However, the uptake is lower in older adolescents. One study also showed that especially non-college adolescents bear the disease burden as the vaccine rates are lower (38-57%) compared to college-bound adolescents (90%-100%) [11]. A study identifying factors associated with MenACWY uptake among adolescents showed that younger adolescents more often received MenACWY vaccination compared to older adolescents [12]. This was largely explained by the difference in healthcare utilization (i.e. older adolescents have fewer preventive care visits and interaction with non-paediatric healthcare providers). This indicates that unique strategies might be necessary to increase uptake among older adolescents, such as encouraging annual preventive care visits in adolescents aged 16 to 18 years [12]. Another study showed significant influence of state of residence on the likelihood of MenACWY vaccine completion and compliance [13]. This was mainly due to state-level determinants, such as paediatrician-to-children ratio and the proportion of Immunization Information System use among adolescents.

3.8.2 *HPV*

A literature review focused on summarizing all peer-reviewed and grey literature published about determinants of HPV vaccine hesitancy Europe. They state that Europe is increasingly described as a region with the least confidence in vaccination and the safety of vaccines. Determinants differed by country and population groups. Tailored and context-specific interventions are, therefore, essential to improve confidence in HPV vaccination and build public trust [14]. Other studies support this view. For example, a study conducted in the UK focused on the influence of school-level and area-level factors on HPV vaccine coverage [9]. Muslim and Jewish schools had lower coverage compared to schools with no religious character. Also, independent, special schools had lower vaccination coverage compared to state-funded secondary schools. Tailored approaches are necessary to increase HPV vaccine

uptake in Muslim and Jewish schools [9]. A cross-sectional study conducted in Italy focusing on individual factors that influence HPV vaccine hesitancy suggests that communication and education strategies must be undertaken to ensure parents are fully informed and (relevant) HCP should be included to provide information about the risks of contracting HPV infection and vaccine usefulness [15].
A study, indicating that HPV vaccination in the UK will soon be extended to boys and that vaccine uptake for boys might initially be lower in boys compared to girls, examined what would influence parents' (who's child is eligible for HPV vaccination within 3 years) willingness to vaccinate, not vaccinate or remain undecided about vaccinating their child [16]. The results indicated that previous vaccine refusal (in general) was the strongest predictor of not wanting the HPV vaccine. However, awareness of HPV and HPV vaccine as well as a positive attitude were associated with the decision to vaccinate. This suggests that there is a need for the public to become more aware through public health campaigns [16].
Another study focusing specifically on HPV vaccination for boys in Sweden showed that participants were in favour of introducing HPV vaccinations for boys in the NIP [17]. Furthermore, in Slovenia the inclusion of HPV vaccination for boys is planned for schoolyear 2020/2021. The HPV for boys is currently paid by municipalities and the study examined the results on vaccine uptake. The study showed that acceptance of HPV vaccination for boys in Slovenia is adequate (ranging from 25% to 69%) and this will lead to significant results when it is included in the NIP of Slovenia. The current success of the vaccination coverage (i.e. coverage rates are comparable or even higher than those in the NIP for girls) is contributed to excellent local initiatives of several HCP and school medicine specialists [18].

3.9 Literature

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*RIVM publication

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 2019 was highest for HPV (19,400 DALYs (75% among women)), invasive pneumococcal disease (9,500 DALYs/year), pertussis (2,600 DALYs/year), rotavirus infection (1,100 DALYs/year), invasive *Haemophilus influenzae* disease (970 DALYs/year), and invasive meningococcal disease (890 DALYs/year).
- For most diseases, the estimated burden in 2019 was comparable to the estimated burden in 2018. The disease burden of invasive pneumococcal and meningococcal disease was lower in 2019, whereas the burden of HPV (for females), measles and pertussis was somewhat higher in 2019 than in 2018.

4.2 Tables and figures

Table 3.1 Estimated annual disease burden in DALYs in 2015–2019, and DALYs per 100 infections in 2019 in the Netherlands (with 95% uncertainty intervals) [1, 2]

Disease	DALYs (95% uncertainty interval)					DALYs/100
	2015	2016	2017	2018	2019	infections
Diphtheria	4 (3–5)	2 (2–3)	4 (3–4)	3 (3–4)	0 (0–0)	n/a
Hepatitis A virus infection	43 (27–72)	44 (27–73)	200 (120–340)	100 (62–170)	90 (55–150)	11 (8–15)
Hepatitis B virus infection (acute)	100 (95–110)	180 (170–190)	150 (140–160)	130 (120–140)	120 (110–120)	23 (21–23)
Human papillomavirus infection[a]						
- Females	12,000 (11,200–12,800)	13,200 (12,400–14,000)	12,900 (12,100–13,800)	13,800 (13,000–14,700)	14,600 (13,800–15,400)	n/a
- Males	4,900 (4,100–5,900)	5,300 (4,400–6,400)	5,200 (4,200–6,300)	5,400 (4,400–6,400)	4,800 (4,000–5,800)	n/a
Invasive *H. influenzae* disease	840 (800–890)	860 (800–910)	980 (930–1,000)	1,000 (960–1,100)	970[b] (920–1,000)	380 (360–400)
Invasive meningococcal disease	560 (440–700)	880 (730–1,000)	1,100 (970–1,300)	1,100 (970–1,300)	890[c] (740–1,100)	530 (490–580)
Invasive pneumo-coccal disease	10,900 (10,200–11,500)	9,800 (9,200–10,500)	9,800 (9,200–10,400)	10,800 (10,100–11,400)	9,500[d] (8,900–10,100)	360 (340–380)
Measles	1 (1–1)	1 (1–1)	3 (2–3)	5 (4–5)	16 (15–18)	2 (2–2)
Mumps	0.7 (0.6–0.7)	0.5 (0.5–0.6)	0.4 (0.3–0.4)	0.6 (0.5–0.6)	1 (1–1)	0.4 (0.4–0.4)
Pertussis	2,700 (2,500–2,900)	1,500 (1,400–1,600)	2,000 (1,900–2,200)	2,000 (1,900–2,100)	2,600 (2,500–2,800)	1 (1–1)
Poliomyelitis	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	n/a
Rabies	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	n/a
Rotavirus infection	1,300 (520–2,500)	670 (280–1,300)	1,100 (440–2,200)	1,200 (470–2,400)	1,100 (440–2,300)	0.5 (0.3–1)
Rubella	0.06 (0.04–0.08)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	n/a
Tetanus	9 (7–10)	2 (2–2)	0.6 (0.5–0.8)	1 (1–1)	0 (0–0)	n/a

DALY= disability-adjusted life years

n/a = not applicable; no cases occurring in 2019 or unknown number of infections (HPV)

[a] To estimate the burden, the numbers of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV were used. The most recent year of available data on the incidence of anogenital warts and high-grade cervical lesions was 2016 and 2018, respectively. Therefore, the incidence rate of anogenital warts for 2016 was carried forward to 2017–2019 and the incidence rate of high-grade cervical lesions for 2018 was carried forward to 2019.

[b] Proportion caused by the vaccine-preventable type b in 2019: 28%.

[c] Proportion caused by the vaccine-preventable type C in 2019: 3%; proportion caused by type B in 2019: 59%; proportion caused by type W in 2019: 29%.

[d] Proportion caused by the vaccine-preventable types 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F in 2019: 4%.

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

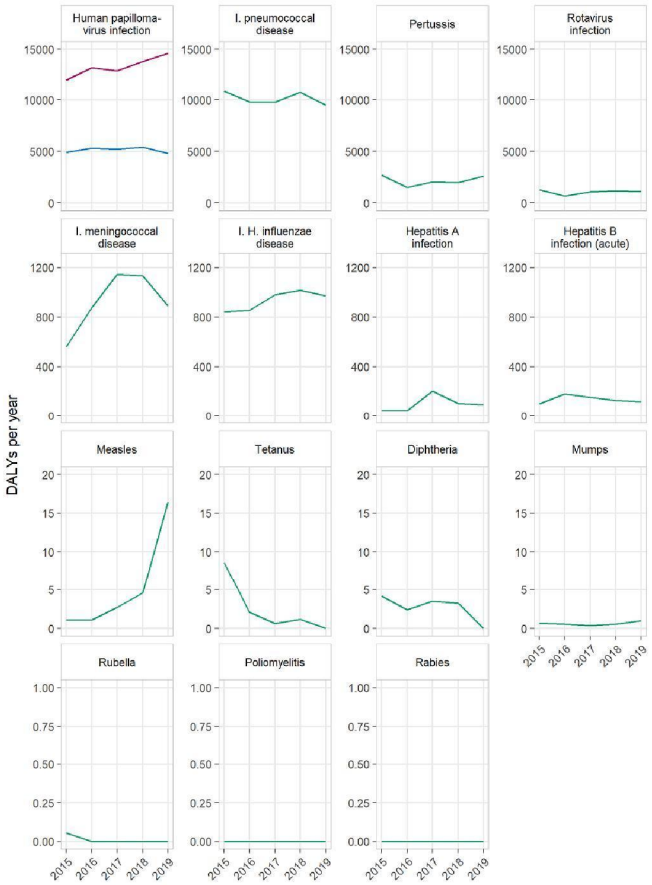

Figure 3.1 Estimated annual disease burden in DALYs in 2015–2019 in the Netherlands [1, 2]
1. Vaccination against rabies, hepatitis A and rotavirus infection is not included in the NIP.
2. For the three invasive diseases, a vaccine was only available against certain serotypes: Haemophilus influenzae serotype b (Hib), meningococcal ACWY 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 y-axes are not the same for all diseases.
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 2015–2019. We present the same estimates published in the 'State of infectious diseases in the Netherlands, 2019', 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 3.1 shows the estimated DALYs per year in the period 2015–2019 and the DALYs per 100 infections in 2019 (a measure of the disease burden at individual patient level) in the Netherlands, with 95% uncertainty intervals. For diphtheria, poliomyelitis, rabies, rubella, and tetanus, the estimated disease burden in 2019 was zero because no cases were reported. For mumps, the disease burden in 2019 was estimated to be very low, while the highest burden was estimated for HPV infection, followed by invasive pneumococcal disease, pertussis, rotavirus infection, invasive *Haemophilus influenzae* disease, and invasive meningococcal disease.

The incidence of pertussis and rotavirus infection is known to surge every few years (Figure 3.1). For most diseases, the estimated burden in 2019 was comparable to the estimated burden in 2018. The burden for invasive pneumococcal and meningococcal disease was lower whereas the burden of HPV (for females), measles and pertussis was somewhat higher in 2019 compared with 2018. The burden for invasive meningococcal disease in 2019 was lower because of the considerable decline in the number of patients (from 103 reported cases in 2018 to 62 reported cases in 2019) caused by serogroup W (see also Chapter 7.6). The proportion of the burden due to serogroup W in the total burden of invasive meningococcal disease decreased from 42% in 2018 to 29% in 2019. For invasive pneumococcal disease, both the number of cases caused by vaccine types as well as non vaccine types decreased. The proportion of the burden due to vaccine types in the total burden of invasive pneumococcal disease decreased from 10% in 2018 to 4% in 2019. The higher burden of invasive pneumococcal disease in 2018 may be related to the severe influenza epidemic in that season. The higher measles burden was caused by an increase in measles incidence in 2019 compared to previous years, including a local measles outbreak in Urk.

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 2015–2019, which means that the disease burden of (chronic) hepatitis B cases infected prior to this period is not included.

4.4 Literature

4.1.1 *References*

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*RIVM publication

5. Adverse events

J.M. Kemmeren

5.1 Key Points

- In 2019, Lareb received 2,009 reports of a total of 7,378 adverse events following immunization (AEFIs). Compared to 2018, the number of reports increased by 32%, while the number of reported AEFIs increased by 42%. The increase in number of reports is mainly due to the catch-up campaign of MenACWY vaccination in adolescents. The number of reported AEFIs per report remained stable.
- 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) [1]

Vaccines	Total 2018	**Total 2019**	2m	3m	4m	5m	11 m	14 m	4yr	9yr	12-13yr	14-18yr	Pregnant women	Other/ Unknown
Vaxelis® + Synflorix®		**278**	139	50	37	22	23							7
Infanrix hexa® + Synflorix®	457	**192**	24	3	19	17	100							29
Vaxelis®		**99**	13	48	16	5								17
Synflorix®	9	**5**	1	2			1							1
Infanrix hexa®	118	**40**	4	12	5	2	4							13
MMRvaxPro® + Nimenrix®	173	**227**						216						11
MMRvaxPro®	16	**39**						13		3				23
MMRvaxPro® + NeisVac-C®	85													
NeisVac-C®	1													
Boostrix Polio®	326	**313**							307					6
Infanrixhexa® zonder Hib		**13**							9					4
MMRvaxPro® + Revaxis®	103	**118**								117				1
Revaxis®	7	**12**								8				4
Cervarix®	81	**104**									75	28		1
Nimenrix®	121	**520**						7				469		44
Boostrix®		**9**											9	
Other	22	**40**												40
Total 2019		**2009**	181	115	77	46	128	236	316	128	75	497	9	201
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

Table 5.2 Reported severe adverse events per vaccination moment in 2019 [1]

	2m	3m	4m	5 m	11 m	14 m	4yr	9yr	12y r	14y r	Pregna nt wome n	Unknow n /other	Total
Rash, eczema	**10**	**8**	**9**	**4**	**8**	**115**	**14**	**21**	**3**	**24**	**0**	**30**	**246**
Respiratory symptoms, decreased consciousness	**25**	**10**	**13**	**4**	**6**	**7**	**5**	**14**	**8**	**45**	**0**	**12**	**149**
Collapse, (pre)syncope, drop attacks	3	2	2	0	0	1	2	13	7	34	0	3	67
Apnoea, dyspnoea, irregular breathing	10	4	5	3	6	6	3	1	1	11	0	6	56
Hypotonic-Hyporesponsive Episode (HHE)	8	3	5	1	0	0	0	0	0	0	0	2	19
Breath holding spells	3	1	0	0	0	0	0	0	0	0	0	0	4
Apparent Life Threatening Event (ALTE)	1	0	1	0	0	0	0	0	0	0	0	1	3
Extensive swelling of vaccinated limb (ELS)	**3**	**5**	**3**	**0**	**7**	**2**	**45**	**1**	**0**	**7**	**0**	**14**	**87**
Convulsions, epilepsy	**3**	**3**	**2**	**7**	**8**	**17**	**3**	**3**	**4**	**8**	**0**	**8**	**66**
(febrile) Convulsions, seizures	2	2	1	4	7	15	2	1	0	5	0	5	44
(febrile) Delirium	0	0	0	0	0	0	1	1	0	0	0	0	2
Epilepsy, status epilepticus	1	0	0	1	0	1	0	0	1	1	0	0	5
Ataxia, spasms, tics	0	1	1	2	1	1	0	1	3	2	0	3	15
Fever ≥40.5°C ≤42°C	**2**	**0**	**2**	**4**	**4**	**20**	**4**	**3**	**1**	**0**	**0**	**9**	**49**
Allergic reaction, anaphylaxis	**1**	**1**	**1**	**1**	**3**	**13**	**9**	**7**	**2**	**5**	**0**	**14**	**57**
Persistent crying	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**
Skin discolouration	**10**	**7**	**4**	**3**	**1**	**1**	**1**	**0**	**0**	**1**	**0**	**0**	**28**
Abscess	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**
Injection site abscess	0	0	0	0	1	0	0	0	0	0	0	0	1
Lymph node abscess	0	0	0	0	0	0	0	0	0	0	0	0	0
Abscess of salivary gland	0	0	0	0	0	0	0	0	0	0	0	0	0
Immune mediated disorders	**0**	**0**	**0**	**0**	**0**	**2**	**1**	**0**	**0**	**2**	**0**	**0**	**5**
Diabetes Mellitus	0	0	0	0	0	0	1	0	0	1	0	0	2
Acute haemorrhagic oedema of infancy	0	0	0	0	0	0	0	0	0	0	0	0	0
Immune thrombocytopenic purpura (ITP)	0	0	0	0	0	1	0	0	0	0	0	0	1
Kawasaki's disease	0	0	0	0	0	1	0	0	0	0	0	0	1
Juvenile idiopathic arthritis	0	0	0	0	0	0	0	0	0	0	0	0	0
Dehydration	**0**	**0**	**0**	**0**	**1**	**3**	**0**	**0**	**0**	**0**	**0**	**0**	**4**
Death*	**2**	**0**	**1**	**0**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**5**
SIDS	1	0	1	0	0	0	0	0	0	0	0	0	2
Other	1	0	0	0	1	1	0	0	0	0	0	0	3
Encephalitis, meningitis	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**4**	**0**	**1**	**6**
Postural orthostatic tachycardia syndrome	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Vaccine failure	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

Chronic fatigue	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Venous thrombosis	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Chronic arthritis	**0**	**0**	**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**	**0**	**0**

* For a full descriptions of the causes of death: see yearly report of 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 2019, Lareb received 2,009 reports with a total of 7,378 AEFIs (Table 5.1) [1]. Compared to 2018, the number of received reports increased by 32.3% (1,519 in 2018), while the number of reported AEFIs increased by 41.7% (5,208 in 2018). The increase in the number of reports received can be explained by the catch-up campaign of the MenACWY vaccination in adolescents of 14-18 years of age in 2019. Most reported AEFIs were injection site reactions (n=2,063), fever (n=821), headache (n=295, from which 197 after the MenACWY vaccination during the catch-up campaign) and crying (n=251). Of the reports, 95 (4.7%) were classified as serious.
The number of reports per dose and vaccine are mostly within the range of the last eight years (see Table 5.1), although there appears to be a shift in number of reports after vaccination in the first year of life. This may be related to the introduction of maternal vaccination in the Netherlands in 2019 and a change in DKTP-Hib-hepB vaccine used in the NIP [1].
For infants aged 11 months, the number of reports decreased for the first year since 2015. The number of reports in infants aged 14 months is also decreased. The decrease in the number of reports after administration of DTP-IPV at the age of 4 years which started in 2017 (n=387; n=326 in 2018) continued in 2019 (n=316), whereas an increasing trend is seen after the vaccination at 9 years of age. The decrease of number of notifications received after the administration of the HPV vaccine seems to have to stopped in 2019 (see Table 5.1). Twenty-eight reports were received after HPV vaccination in girls of 14-18 years of age. Normally HPV vaccination takes place at the age of 12 years. As a result of the invitations for the MenACWY vaccination of the 14-18 year olds, some youth health care organizations invited girls to still get the HPV vaccination.
The increasing trend in number of reports after vaccination on a different or unknown vaccination moment which started in 2017 (n=76; n=167 in 2018), continued in 2019 (n=201). This was mainly observed for vaccinations in the first years of life, and after vaccination with Nimenrix (n=44) which frequently is administered outside the NIP and catch-up campaign. Reasons for the increasing trend for the other vaccines are unknown
The number of reported AEFIs per report remained stable (3.7% in 2019 vs 3,9% and 3.4% in 2017 and 2018, respectively).

Table 5.2 summarizes 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 (n=59 in 2017 and n=21 in 2018) did not continue in 2019 (n=45). Furthermore, an increase in notifications of rash was seen after the vaccination at the age of 14 months (n=94 in 2017, n=95 in 2018 vs n=115 in 2019). The introduction of Nimenrix in spring 2018 does not appear to be responsible for this increase as no increase was observed in 2018. The increase may be a result of natural variation over the years, which will be monitored.
No reports of postural orthostatic tachycardia syndrome (POTS) and chronic fatigue syndrome (CFS) after HPV vaccination were received. Fatigue after HPV vaccination was reported 13 times, which is comparable to 2018 (n=18) and considerably less compared to 2017 (n=30).
Overall, no new signals of disturbing adverse events were found.

5.3.2 *Signals*

5.3.2.1 Lymphadenopathy, urticaria and febrile seizures after vaccination with Nimenrix®

In 2019, Lareb published three signals related to reports about lymphadenopathy, urticaria and febrile seizures, respectively, after vaccination with Nimenrix® [2-4]. Analyzes of these reports show that swollen and sometimes painful lymph nodes and febrile seizures are AEFIs that may occur. Febrile seizures have only been reported in the children who received the vaccination at 14 months of age. The appearance of an itchy rash and urticaria may also be a side effect. This AEFI may be related to a hypersensitivity reaction. These AEFIs are known side effects of Nimenrix®, but are not yet explicitly included in the package leaflet of this vaccine.

5.4 **International Developments**

5.4.1 *Non vaccine-specific adverse events*

The growing number of available vaccines that can be potentially co-administered makes the assessment of the safety of vaccine co-administration increasingly relevant but complex. A systematic review included fifty studies which compared co-administered vaccines versus the same vaccines administered separately. The most frequently studied vaccines included quadrivalent meningococcal conjugate (MenACWY) vaccine, diphtheria and tetanus toxoids and acellular pertussis (DTaP) or tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccines, diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B, inactivated poliovirus and *Haemophilus influenzae* type b conjugate (DTaP-HepB-IPV/Hib) vaccine, measles, mumps, and rubella (MMR) vaccine, and pneumococcal conjugate 7-valent (PCV7) or 13-valent (PCV13) vaccines. Of this, 16% (n = 8) of the studies reported significantly more adverse events following immunization (AEFI) while in 10% (n=5) significantly fewer adverse events were found in the co-administration groups. Statistically significant differences between co-administration and separate administration were found for 16 adverse events, for 11 different vaccine co-administrations. This study indicated that differences in safety of vaccine co-administrations compared to separate vaccine administrations may exist, particularly for more common, less severe AEFI. However, the authors concluded that the safety of vaccine co-administrations compared to separate vaccine

administrations is inconclusive and there is a paucity of large post-licensure studies addressing this issue [5].

5.4.2 *Vaccines targeting diseases included in the current NIP*

5.4.2.1 MMR/MMRV

Several studies demonstrated the safety of the MMR/MMRV vaccine [6-8], although more evidence is needed to assess whether the protective effect of MMR/MMRV could wane with time since immunization [6]. An early MMR dose in infants younger than 9 months or 2-dose measles schedule at 6 and 12 months also showed to be safe [9, 10]. Live attenuated vaccine safety was demonstrated in HIV infected children (MMR) [11] and adult patients receiving hematopoetic stem cell transplantation (MMRV) [12]. An increase in the risk for ITP was observed in children receiving the varicella and MMR vaccines concomitantly (IRR 1.70; 95% 1.02-1.18) [13], but erythema multiforme, Steven Johnson syndrome, and toxic epidermal necrolysis were rarely reported after childhood vaccines (e.g. MMR vaccination) [14]. One case report was published about a 4-years-old boy who was admitted with rash and documented disseminated varicella infection 5 weeks after MMRV vaccination [15]. This illustrates what is still unknown about the risk-to-benefit ratio of live viral vaccination in any individual transplant recipient.
A systematic review of pregnancy related AEs following rubella vaccination did not demonstrate an evidence that congenital rubella syndrome is caused by rubella-containing vaccines. However, transplacental vaccine virus infection can occur [16], although the risk/benefit balance is in favor of vaccination. The data confirmed that inadvertent vaccination during pregnancy was not an indication for termination of pregnancy.
Several studies demonstrated that co-administration of MMRV and MenC conjugate vaccines did not have a negative impact on the safety of either vaccines, as concluded in a review by Bonanni [17]. A preclinical study of safety and immunogenicity of combined rubella and HPV vaccines in mice showed that a good safety profile of this combined vaccine [18]. Such a vaccine can be of great value to females above 20 years in low income countries to increase vaccine uptake after clinical testing.

5.4.2.2 Pneumococcal vaccine

A phase II trial showed the safety of a novel PCV12 conjugate vaccine [19]; the overall incidence of solicited systemic adverse events was even lower than in the comparator PCV13 group. A good safety profile was also found in several studies to the safety of PCV13 [20, 21], even in HIV infected adults [22] and patients with monoclonal gammopathy of undetermined significance [23]. Furthermore, no evidence was found of an association between PCV13 vaccination and Kawasaki disease onset in the 4 weeks after vaccination nor of an elevated risk extending or concentrated somewhat beyond 4 weeks [24]. A phase I study showed that vaccination with PCV20 was well tolerated in healthy adults. A study with PPV23 vaccine confirmed the safety of this vaccine in elderly people with chronic lung disease [25], although self-limited local and systemic reactions were more frequent after the second and third vaccinations than after the first vaccination. One review described that PCVs are safe for use in nephrotic patients [26].

Two phase I studies were conducted to assess the safety of novel pneumococcal vaccines that are affordable for resource-limited settings. Both investigational vaccines (wSp and SIIPL-PCV) were well-tolerated and had an acceptable safety profile [27, 28]. In a phase IIb trial a novel dPly/PhtD vaccine was well tolerated in Native American infants [29].

5.4.2.3 Meningococcal ACWY vaccine

Three prelicensure trials were published about the safety of MenACWY-TT. All showed a good reactogenicity profile in adolescents and/or adults [30-32]. The safety profile of this vaccine was also demonstrated regardless of age, primary versus booster vaccination, concomitant vaccine administration or in children primed with MenC vaccine [33-35]. The safety of MenACWY-CRM vaccine in all age groups was also demonstrated in several studies [36-38]. One study assessed the baseline prevalence estimates of spontaneous abortions, preterm births, low weight births, and major congenital malformations among women inadvertently exposed to MenACWY-CRM during pregnancy period [39]. These estimates appeared to be comparable with US background prevalence estimates.
The concomitant administration of meningococcal vaccines with other vaccines in adolescents and adults was reviewed by Alderver et al [40]. In general, data suggest that these vaccines can be safely co-administered with other vaccines.
In an exploratory study the safety of 1 and 2 doses of an MenAC-TT vaccine in toddlers was demonstrated [41]. A review about the safety profile of a MenA vaccine showed that the incidence of AEs after MenA vaccination was for lower in campaigns then in clinical trial studies [42]. This systematic review highlights the magnitude of the difference between IR of AEFI as evaluated in the controlled setting of clinical trials and more pragmatic approach of mass vaccination campaigns.

5.4.2.4 DTaP-IPV-HBV-Hib

Two studies showed the safety of pentavalent DTwP-HBV-Hib combination vaccine [43, 44] and one study demonstrated the safety of DTaP-IPV/Hib vaccine [45]. Another study showed the safety profile of a fully liquid, ready to use, hexavalent vaccine, which was similar to that of several approved vaccines [46].
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 [47-50]. One of the studies found an association between infant exposure to Tdap during pregnancy an ankyloglossia and neonatal erythema toxicum diagnosis [47]. Both were supposed to be a result of residual confounding, or spurious associations to the large number of endpoints. Four overviews confirmed the safety of maternal Tdap immunization [51-54], although one advised to optimize the timing of vaccination in pregnancy. There is currently no evidence of an association between vaccination during pregnancy and neonatal seizures [54]. There is also no evidence for higher frequency of clinically relevant sequelae due to an increased risk of fever and chorioamnionitis after maternal pertussis vaccination [51].

5.4.2.5 HPV

Several studies and reviews demonstrated the safety of HVP vaccines [55-57]. No evidence of increased infertility [58], CRPS, chronic fatigue, POTS or other forms of dysautonomia [59], Guillain-Barre syndrome [60], autoimmune and other rare diseases [61] were published. The concomitant administration of other vaccines along with HPV vaccines was acceptable [62] and inadvertent HPV vaccination during pregnancy was not associated with significantly greater risks of adverse pregnancy outcomes [63].Two studies proved that HPV vaccine is safe in HIV infected people [64, 65]. Another study revealed a different distribution pattern of AEs across gender and age subgroups and correlated patterns across various AEs after HPV vaccination [66]. However, further clinical studies are needed to understand the heterogeneity of these AEs and the biological pathways among the statistically correlated AEs.
A descriptive study that AEs-reporting rates for HPV immunization have decreased considerably, perhaps by a reduction and stabilization of reporting over time or decreased media attention [67]. A study in Denmark showed that despite an official aim of homogenous case management, reporting of suspected AEs was incomplete with large regional difference [68]. This observation represents an important caveat in interpreting data from AEs reporting, in particular wen these data are used for research or policymaking.

5.4.2.5.1 2vHPV, 4vHPV, 9vHPV vaccines
Results from studies on the safety of 2vHPV did not reveal new or unexpected safety concerns in female and/or male adolescents [69-71], and in children of 4-6 years of age [72]. Also 4vHPV vaccine showed to be well-tolerated without new safety signals [73, 74], even by concomitant administration of 4vHPV, Tdap and MenACWY-CRM in adolescents [75]. The findings of a phase I study suggest that 4vHPV vaccination may be safely administered to women post-allogeneic transplant to potentially reduce HPV infection and related neoplasia [76]. Five studies reported no new or unexpected safety concerns or reporting patterns of 9vHPV with clinically important AEs were detected [77-81].

5.4.2.5.2 New vaccines
A phase III clinical trial was conducted to evaluate the efficacy, safety, and immunogenicity of a novel Escherichia coli-produced bivalent HPV-16/18 vaccine [82]. In the per-protocol cohort, the side effects were mild and no vaccine-related serious adverse events were noted. This novel vaccine showed to be well tolerated.

5.4.3 *Other potential future target diseases*

5.4.3.1 Meningococcal B

In Canada, active safety surveillance identified an unexpected increase in nephrotic syndrome incidence following 4CMenB vaccination [83]. The greater risk in vaccines had wide confidence intervals with the lower limit including or just above the null value (i.e. RR 8.3; 95% CI when compared to pre-vaccination period and RR 3.6; 95% CI 0.7-11.8 when compared with region without mass vaccination). The temporal association with vaccination may be explained by other causes and/or chance clustering of a rare event unrelated to vaccination. Another study found that 4cMenB is associated with AEs (temperature >37.5 °C, needed partial septic screens, needed intravenous antibiotics) in

hospitalized preterm infants [84]. Prophylactic paracetamol administration attenuates this. Nicolosi et al demonstrated that 4CMenB is almost well tolerated, with a low incidence of severe AEs. The only AEFI that has been perceived as severe by a significant number of parents and caregivers was the refusal to move the extremity (described as severe in 12.1% of all the vaccinated children). They also showed that the occurrence of AEs is similar within healthy children and children with chronical medical conditions [85]. A randomized trial in Canada of 2 schedules of 4CMenB vaccine in adolescents and young adults showed that the rate of unsolicited AEs did not differ by dosing schedule or dose. One participant had a serious AE unrelated to vaccination [86]. After more than 3 million 4CMenB doses administered to infants, no safety concerns have been identified in the UK [87].

5.4.3.2 Varicella

The safety of live attenuated varicella vaccine was demonstrated in a trial in China [88]. A comprehensive 22-year review confirms the overall safety for this vaccine, with no new safety concerns identified [89]. AEs occurred with similar frequency and severity between HIV-unexposed and HIV-exposed uninfected children, except for more systemic AEs after varicella vaccination in HIV-unexposed than in HIV-exposed uninfected children (57% vs 29%; p=0.007) [90]. The underlying reason for this difference remains unclear. In Taiwan, a small risk of incidental pneumonia associated with varicella vaccine in the 6th week after immunization was detected (IRR 1.10; 95%CI 1.02-1.18) [13]. There was no increase in the risk of other pre-specified adverse events (i.e. ITP, meningitis, encephalitis, and ischemic stroke). Harrington presented two adolescents with reactivated vaccine Oka meningitis, one immunocompetent and one immunocompromised, both of whom received 2 doses of varicella vaccine many years before as children [91]. This finding of the potential of vaccine Oka varicella to reactivate may be important in future diagnosis and care of patients with meningitis and encephalitis.
In a double-blind, randomized, multicenter study, the safety and tolerability of a refrigerator-stable varicella vaccine was similar to that of the frozen formulation [92].

5.4.3.3 Herpes Zoster

No safety concerns were identified for live-attenuated herpes zoster vaccination, even in patients with rheumatoid arthritis, in patients with systemic lupus erythematosus, or patients with solid tumour malignancies receiving chemotherapy or other underlying chronic diseases [93-97]. A methodological study to test the self-controlled tree-temporal scan statistic in older adults also demonstrated consistent results with local-site reactions and other known, generally mild, vaccine-associated AEs and a favorable safety profile for live-attenuated herpes zoster vaccine [98].
Recombinant zoster vaccine is associated with local and systemic reactions that is significantly greater than observed with commonly used vaccines [99]. Several studies confirmed these findings although no safety concerns were identified [100-102], even when co-administered with Tdap [103]. The safety profile of recombinant zoster vaccine was not impacted when given to adults who received previously live-attenuated herpes zoster vaccine [104]. In addition, no safety concerns

arose after recombinant zoster vaccination in patients with inflammatory bowel disease and in chronically immunosuppressed adults [105-107]. A Cochrane Review assessed the safety of vaccination for preventing herpes zoster in older adults [108]. In this review it was concluded that both live-attenuated herpes zoster vaccines and recombinant zoster vaccines produce systemic and injection site adverse events of mild to moderate intensity.

5.4.3.4 Hepatitis A

In Australia, a combined hepatitis A and typhoid vaccine is available, but licensed for use from age 16 years. This year, a study showed that this vaccine is also well tolerated in children aged 2-16 years and the risk of adverse events is similar to those receiving concurrent monovalent vaccines [109]. Another study showed that hepatitis A vaccination during pregnancy was not associated with an increased risk for a range of AEs examined among pregnancies resulting in live births. However, an identified association between maternal hepatitis A and small-for-gestational age infant outcomes, while likely due to unmeasured confounding, warrants further exploration [110].

5.4.3.5 Hepatitis B

Hepatitis B vaccination showed to be safe and well tolerated in patients with rheumatoid arthritis, patients with type 2 diabetes, patients with chronic kidney disease not yet on maintenance dialysis, and HIV infected adults [111-114]. Stowe et al evaluated the epidemiological evidence for a relationship between vaccination and neurological diseases. They found no evidence for the hypothesized relationship between multiple sclerosis and hepatitis B vaccination [60].

5.4.3.6 Rotavirus

Several studies showed an increased risk for intussusception after rotavirus vaccination [115-118]. However, the overall risk for intussusception in the first year of life seems not to be increased or even decreased [115, 117] and a nonsignificant decrease in intussusception was found in the US in fully rotavirus vaccinated children followed up to the age of 2 years [119]. In Ireland, no increase in the national crude incidence rate of intussusception was observed after inclusion of rotavirus vaccination in the NIP [120] and the risk of intussusception in the 21 days after the first or second dose of monovalent rotavirus vaccination was not higher than the background risk among South Africa infants [121]. These findings confirm the conclusion of a study in New Zealand, where no change in the overall incidence of intussusception or clear change in patterns of cases was seen, although intussusception cases did occur within risk period immediately post vaccine [122]. An overview of several quantitative benefit-risk models showed across all included studies, the benefits of rotavirus vaccination that largely exceed the increased risk of intussusception [123]. A study in LMICs found a favorable benefit-risk profile for rotavirus vaccines which caused fewer excess intussusception deaths than the schedules currently recommended by WHO [124]. Results of a systematic review and meta-analysis suggest that monovalent, pentavalent, monovalent human-bovine, oral bovine pentavalent, and human neonatal rotavirus vaccination was not associated with an elevated risk of intussusception among neonates or infants [125]. However, this meta-analyses included

only randomized clinical trials which are inadequate to identify a potential increased risk of rare adverse events such as intussusception [126].
No association was found for rotavirus vaccination and Kawasaki disease [127] and for type 1 diabetes in children [128]. A review concluded that, although data were limited, co-administration of rotavirus and meningococcal vaccines does not appear to interfere with the safety of rotavirus vaccines [129].
New vaccines such as a heat-stable rotavirus vaccine and the trivalent P2-VP8 vaccine were shown to be well-tolerated [130, 131].

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*RIVM publication.

6. NIP-wide research topics

M. Middeldorp

6.1 Key points

- Following implementation of Dutch COVID-19 response measures, the reported incidence of pertussis, invasive pneumococcal disease (IPD), invasive meningococcal disease (IMD), and mumps has decreased.

6.2 Impact of the COVID-19 pandemic on incidence of vaccine preventable diseases in the Netherlands

The reported incidence of pertussis, invasive pneumococcal disease (IPD), invasive meningococcal disease (IMD), and mumps decreased after the implementation of the Dutch COVID-19 response measures. The most likely reason for the reduced incidence of several VPD is reduced transmission as result of social distancing measures and school closure [1]. However, factors like changed healthcare seeking behaviour, diagnostics capacity, and reporting delays may have contributed [2]. The findings suggest that, based on the magnitude of the effects and the timing, it is very likely the measurements initiated in response to the pandemic have reduced the true incidence of several VPDs.

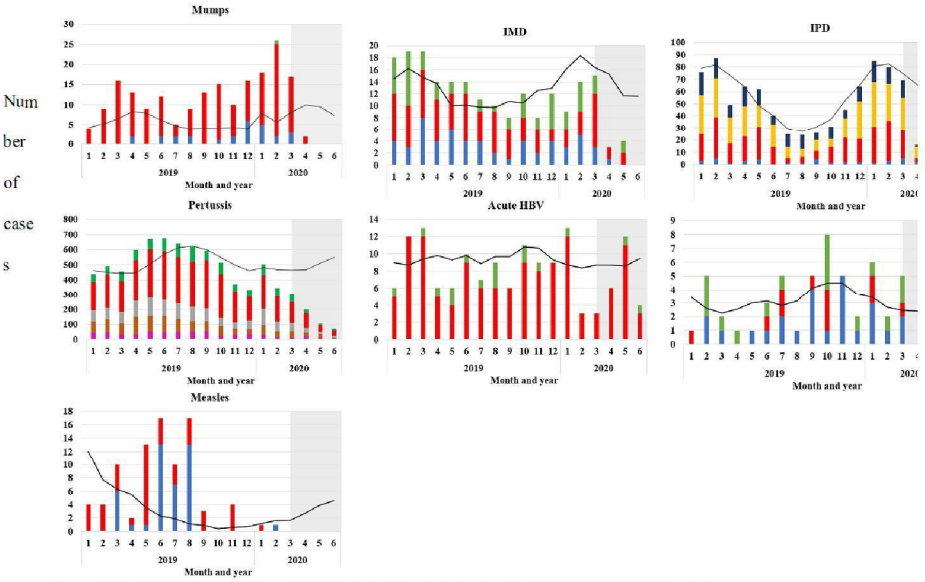

Figure 1. Number of cases per calendar month for mumps, IMD, acute HBV, and Hib among <18, 18-64 and 65+ year-olds, and number of cases for IPD among <18, 18-64, 65-79, and 80+ year-olds in the sentinel surveillance covering 25%

of the Dutch population, and number of cases per month for pertussis among <5, 5-11, 12-18, 18-64, and 65+ year-olds from January 2019 to June 2020 relative to the 5-year moving average. Nationwide control measures in view of the COVID-19 pandemic were taken on 15th of March and are shaded in the figure. From mid-May, some measures were relaxed in the Netherlands.

6.3 Literature

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7. Current National Immunisation Programme

7.1 Diphtheria

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

7.1.1 *Key points*

- In 2019, one possible diphtheria case was reported with unknown vaccination history. Although clinical signs were very suspicious for diphtheria and patient received diphtheria antitoxin as treatment, no Corynebacterium was found.
- In 2020, until June 1st, no diphtheria cases were notified
- A European serosurveillance study showed that a substantial part of 40-60-year-olds had non-protective DT levels. Levels <0.01 IU/ml varied between 4% and 43%. For 0.1 IU/ml, these percentages varied from 23% up to around 80%. The percentage unprotected in the Netherlands was 12.8% (<0.01 IU/ml) and 57.5% (<0.1 IU/ml).

7.1.2 *Tables and figures*

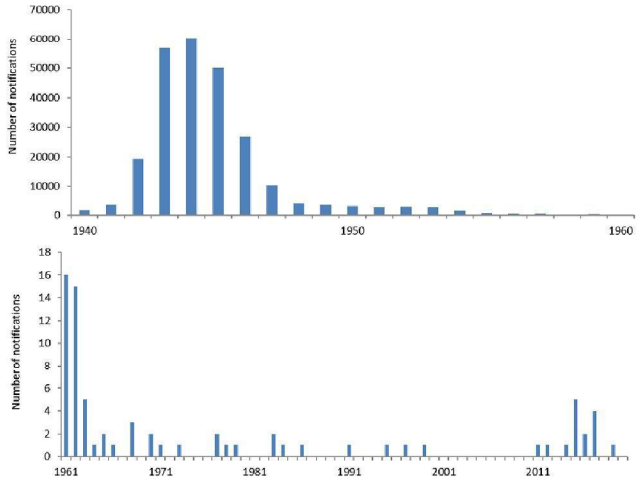

Figure 7.1.1 Diphtheria notifications per year for 1940-1960 (upper part) and 1961-2020(lower part)*
*notifications up to June 2020 are included

Table 7.1.1 Laboratory results of confirmation testing of Corynebacterium diphtheriae and C. ulcerans at RIVM for 2016-2020. Date delivery at 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	NA	2	1	NA	1
2017	9	1	0	0	0	2	NA	2
2018	7	0	0	0	1	2	1	1
2019	7	0	NA	NA	8	0	NA	NA
2020*	2	0	NA	NA	2	0	NA	NA

*up to June 1st, 2020
NA= not applicable

7.1.3 *Epidemiology*

In 2019, one possible case of diphtheria was reported (Figure 7.1.1). It concerned a man with clinical signs of respiratory diphtheria born in 1980 and with unknown vaccination history. De patient received anti diphtheria toxin. However, no Corynebacterium was found. In 2020, up to June 1st, no cases of diphtheria were notified.

7.1.4 *Pathogen*

In 2019, the RIVM received fifteen *C. diphtheria* or *C. ulcerans* strains, of all were from cutaneous samples except one sample from the nose and one case of chronic sinusitis. In 2020 up to June 1, the RIVM received four *C. diphtheria* or *C. ulcerans* strains from cutaneous samples. All strains were PCR negative.
See table 7.1.1 for details on laboratory results for the respective strains.

7.1.5 *International developments*

Within the framework of the EUPertstrain group, a collaboration between European experts on whooping cough, a seroprevalence study in European countries for pertussis, diphtheria and tetanus antibody levels in the 40-60 years age groups has been conducted by the RIVM and funded by ECDC. 18 European countries have participated and collected the requested sera (around 500). Measurement of the antibody levels against pertussis toxin, diphtheria toxoid and tetanus toxin with the MIA has been completed last year establishing a final database of around 30,000 results.
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 (basic immunity) 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

leaving the majority of the 40-60 year age cohorts in Europe without protective immunity against diphtheria (manuscript submitted [1]). The percentage unprotected in the Netherlands was 12.8% (<0.01 IU/ml) and 57.5% (<0.1 IU/ml).

7.1.6 *Literature*

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7.2 *Haemophilus influenzae* disease

M.J. Knol, W. Freudenburg-de Graaf, R. Mariman, G. den Hartog, H.E. de Melker, N.M. van Sorge

7.2.1 *Key points*

- In 2019, the number of cases of *Haemophilus influenzae* type b (Hib) disease was similar to 2018 (39 vs 43 cases). Up to May 2020, 16 Hib cases have been reported, somewhat more than in the same period in 2019 (n=10) but similar to 2018 (n=17).
- In 2019, the incidence of Hib disease was highest among children under 5 years old (2.0 per 100,000). After an increasing trend in incidence observed from 2011 to 2016, the incidence stabilized in the period 2017-2019.
- There were 19 Hib cases in vaccine-eligible children in 2019, of which nine were sufficiently vaccinated, resulting in a Hib vaccine effectiveness estimate of 93%, similar to previous years.
- In 2019, a similar number of cases of non-typable Hi (NTHi) disease were reported as in 2018 (165 vs. 167), suggesting a stabilization of NTHi disease.
- No rise was observed in Hi due to other serotypes.

7.2.2 *Figures*

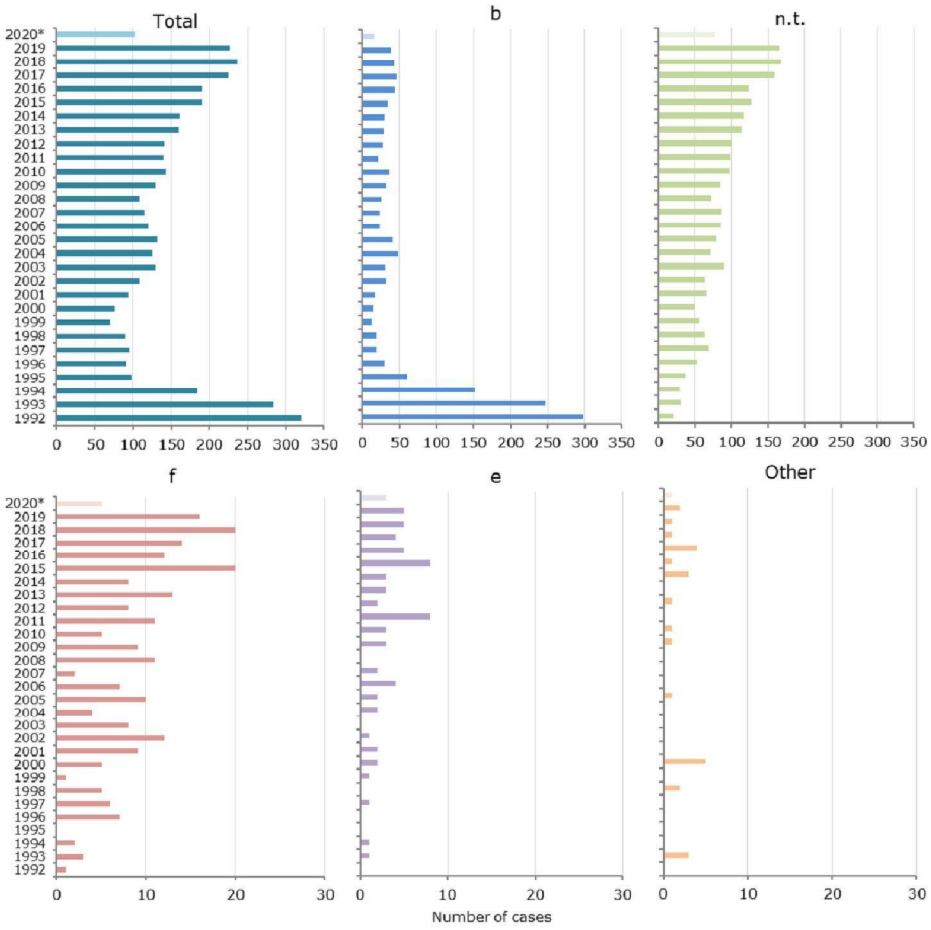


Figure 7.2.1 Number of Haemophilus influenzae cases per serotype, 1992-2020 (*up to May). Note: 'Other' category includes serotype a and serotype d*

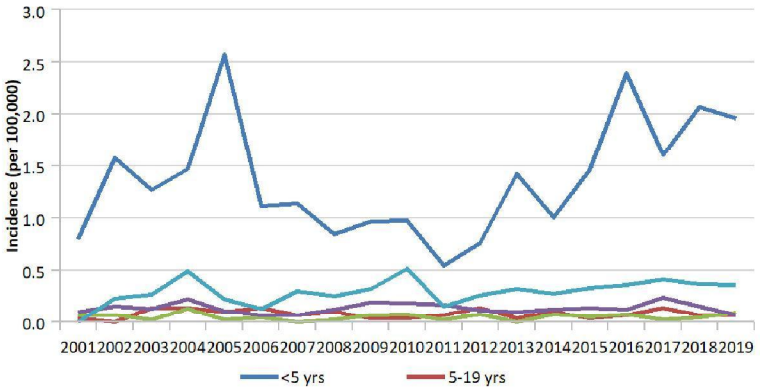


Figure 7.2.2 Age-specific incidence of Haemophilus influenzae type b (Hib) disease, 2001-2019

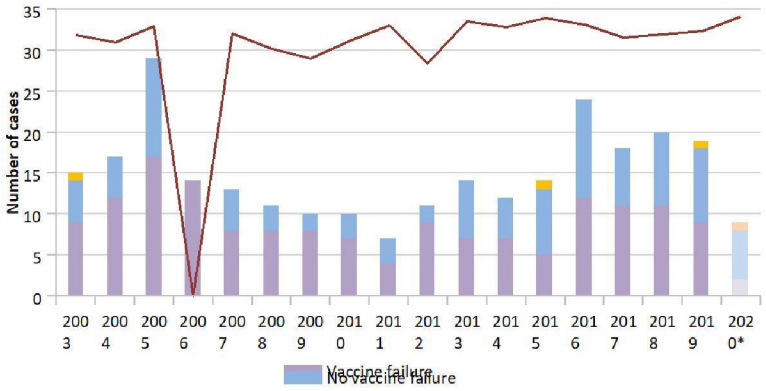


Figure 7.2.3 Number of Haemophilus influenzae type b (Hib) cases in cohorts eligible for vaccination (i.e. born after 1 April 1993) by vaccination status and estimated vaccine effectiveness, 2003-2020 (*up to May). Note: in 2006, VE could not be estimated because 100% of the cases were vaccinated.*

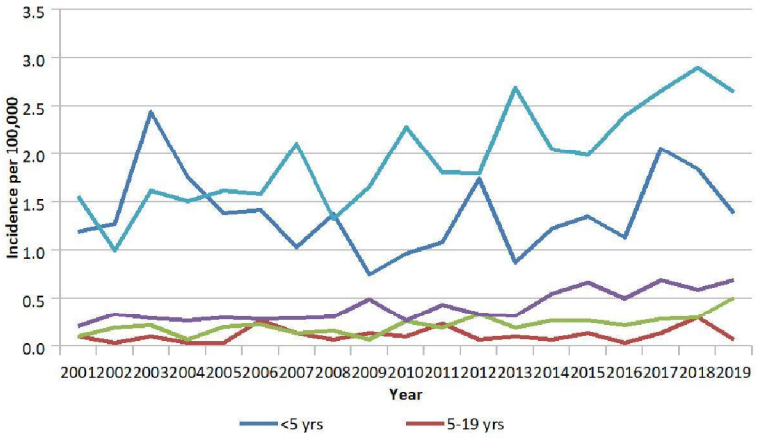


Figure 7.2.4 Age-specific incidence of non-typable Haemophilus influenzae disease, 2001-2019

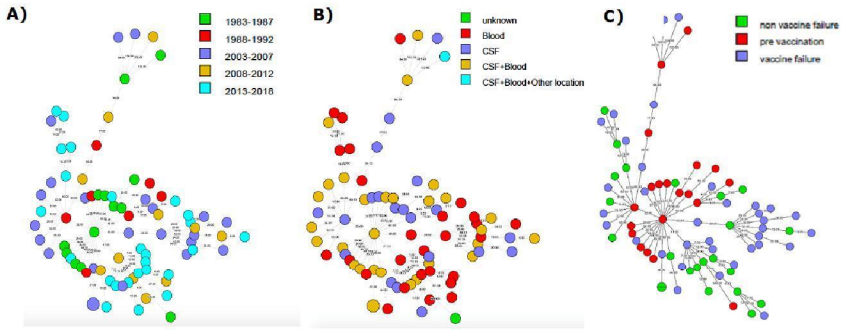


Figure 7.2.5. Genetic relationship between 80 clinical isolates based on cgMLST. Each node of the minimum spanning tree based on cgMLST represents a single Hib isolate. The length of the lines between isolates represents the number of different genes. No clustering of strains by year of isolation (A), invasiveness (B), or vaccination status (C) can be observed.

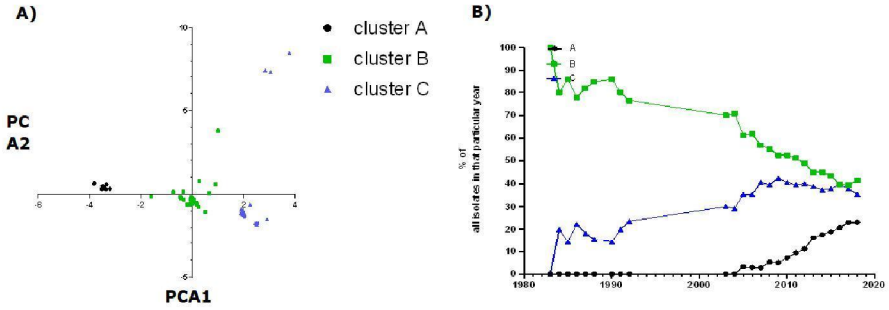


Figure 7.2.6 (A) Unsupervised principal component analysis (PCA) on the total cgMLST (1,738 genes) of 65 isolates with the dominant Sequence Type 6 revealed 3 clusters along components 1 and 2. (B) Relative contribution of each cluster to the total number of isolates analysed in a particular year.

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. Between 2017 and 2019, the number of Hib cases stabilized and in 2019 39 cases were observed (incidence: 0.23 per 100,000) (Figure 7.2.1). The incidence was highest in children <5 years old (2.0 per 100,000; n=17) and has been stable in this age group since 2016 (Figure 7.2.2). Up to May 2020, 16 Hib cases have been reported, somewhat more than in the same period in 2019 (n=10) but similar to 2018 (n=17).
The outcome status was known for 36 and 13 cases in 2019 and 2020, respectively. Of these, two patients of 65 years or older died in 2019.

7.2.3.1.2 Vaccinated cases

In 2019 and 2020 (up to May), 19 and nine Hib cases were reported among cohorts eligible for vaccination, respectively (Figure 7.2.3). Fourteen (50%) of these cases were unvaccinated (nine in 2019, five in 2020), one case was vaccinated once (in 2020) and eleven (42%) were sufficiently vaccinated (i.e. received at least two vaccinations with at least two weeks between the second vaccination and date of diagnosis; nine in 2019 and two in 2020); vaccination status was unknown in two cases. The unvaccinated children were between zero and 17 months old. Most vaccinated cases (seven in 2019 and one in 2020) were younger than five years old. Three (27%) of the vaccinated cases had a known immune disorder.

7.2.3.1.3 Vaccine effectiveness

The estimated vaccine effectiveness (VE) of Hib vaccination using the 'screening method' (see Appendix 1 section 1.1.2.3) was 93% (95%CI

81-97%) in 2019 (Figure 7.2.3). The overall VE for 2003-2020 was 92% (95%CI 90-94%).

7.2.3.2 Non-typable Hi (NTHi) disease

In 2019, 165 cases of NTHi were reported. This was similar to 2018 (167 cases) and 2017 (159 cases), suggesting a stabilization in NTHi disease (Figure 7.2.1). Up to May 2020, 77 cases have been reported, which is lower than the number reported in the same period in 2019 (91 cases), which may be caused by the COVID-19 measures (e.g. social distancing and increased hygiene) which started half of March; especially in April and May 2020 the number of cases was lower than the average in that period in the last five years. In 2019, the incidence was still highest among persons aged 65 and over (2.7 per 100,000; n=88) and children aged under five years (1.4 per 100,000; n=12) (Figure 7.2.4).

7.2.3.3 Disease due to other Hi serotypes

In 2019, five Hi cases with serotype e (Hie) were reported, similar to previous years (Figure 7.2.1). Up to May 2020, three Hie cases have been reported. In 2019, 16 cases of Hif were reported (Figure 7.2.1). Up to May 2020, five Hif cases have been reported. In 2019 and 2020 (up to May), three Hi cases with serotype a have been reported.

7.2.4 *Pathogen*

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

7.2.5 *Current/ongoing research at RIVM*

In 2019, we conducted a study that aimed to elucidate thus far unexplained changes in epidemiology of invasive Hib in the Netherlands by genotypic characterization of clinical isolates. Therefore, we applied Whole-Genome-Sequencing (WGS) to 80 Hib strains isolated from children <5 years diagnosed with invasive Hib disease. From the collection of the Netherlands Reference Laboratory for Bacterial Meningitis, 20 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). A core-genome multi locus sequence typing (cgMLST) scheme, using an in-house scheme consisting of 1738 genes, was used to infer genetic relationships between the isolates. A minimum spanning tree based on cgMLST, showed substantial genetic variation within the Dutch Hib population with an average distance of 35 genes between two neighbouring isolates (range 1–148 genes). There was no clustering in the cgMLST observed based on year of isolation, age, vaccination status, or invasiveness (Figure 7.2.5).
However, in depth analysis of the dominant Sequence Type (ST) 6 (65 out of 80 strains) by principal component analysis (PCA) on the binary transformed cgMLST data revealed three distinct clusters of isolates (Figure 7.2.6A). One cluster that appeared after the introduction of the vaccine is gradually increasing and now comprises one-third of all clinical isolates (Figure 7.2.6B).
Statistical analysis between the three clusters identified 87 genes that were significantly different in any of the comparisons. Among these, genes encoding Immunoglobulin A1 protease autotransporter and Outer membrane protein P1 might be of interest in the context of disease. The preliminary data suggest that the increase in cases up to 2016 might be

caused by expansion of a more successful genotypical Hib cluster. Ongoing research focuses on the genes that drive these clusters.

Data from two population-based cross-sectional serosurveillance studies were used (Pienter-2 study in 2006-2007 and Pienter-1 study in 1995-1996) to assess and compare the concentration of antibodies to the capsular polysaccharide of Hib (1). Post-primary vaccination serum samples from children aged 6–11 months from the Pienter-2 study contained approximately 4-fold lower anti-Hib antibody concentrations than samples from children from the Pienter-1 study. No such difference was found in post-booster samples from children older than 11 months of age. In Pienter-2, the proportion of children aged 6–11 months with anti-Hib antibody concentrations below the putative protective concentration of 0.15 µg/mL was 30%, which was significantly higher than in the Pienter-1 study (12%). Fewer children in the Pienter-2 group developed antibodies able to kill Hib in a serum bactericidal assay compared to the Pienter-1 children. The cause of the lagged response in Pienter-2 children remains uncertain, but lack of natural boosting, interference by the acellular pertussis vaccine, the use of vaccines with more components and a change in the vaccination schedule (starting at two instead of three months of age) may have contributed.

7.2.6 *International developments*

No relevant international developments to report.

7.2.7 *Literature*

1.* Schouls L, Schot C, De Voer RM, Van der Klis F, Knol M, Tcherniaeva I, et al. Lagging Immune Response to Haemophilus influenzae Serotype b (Hib) Conjugate Vaccine after the Primary Vaccination with Hib of Infants in The Netherlands. Vaccines. 2020;8(347).

*RIVM publication

7.3 Hepatitis B

I.K. Veldhuijzen, M. Visser, F. 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 total number of 1205 reported hepatitis B cases, 9% have an acute infection and 91% a chronic infection.
- The incidence of acute hepatitis B notifications remained stable in 2019 at 0.6 per 100,000 population.
- Among both men and women, sexual contact was the most frequently reported risk factor for acute HBV infection.
- In 2019, genotype A continued to be the dominant genotype among acute HBV cases with 58% of 67 genotyped cases, followed by genotype F (18%).
- The number of newly diagnosed chronic HBV infections was 1,079, corresponding to an incidence of 6.2 per 100,000 population.

7.3.2 *Tables and figures*

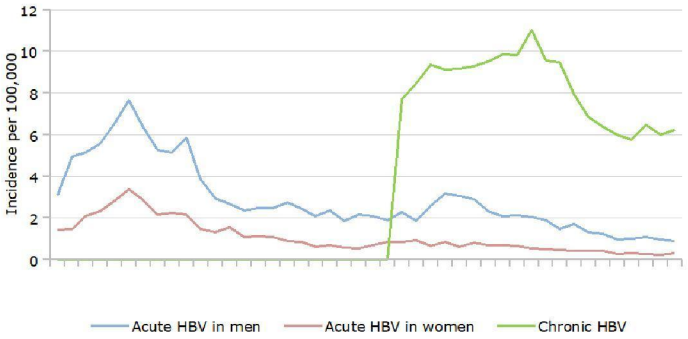


Figure 7.3.1 Incidence of acute HBV infections in men and women in the Netherlands from 1976 and chronic HBV infections from 2000
Source: Osiris

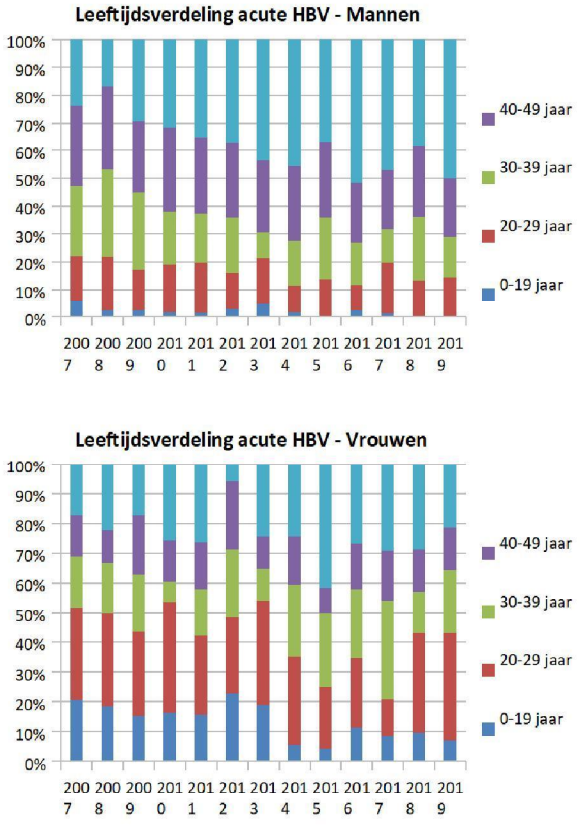


Figure 7.3.2 Age distribution of acute HBV infections in men and women in the Netherlands from 2007 to 2019

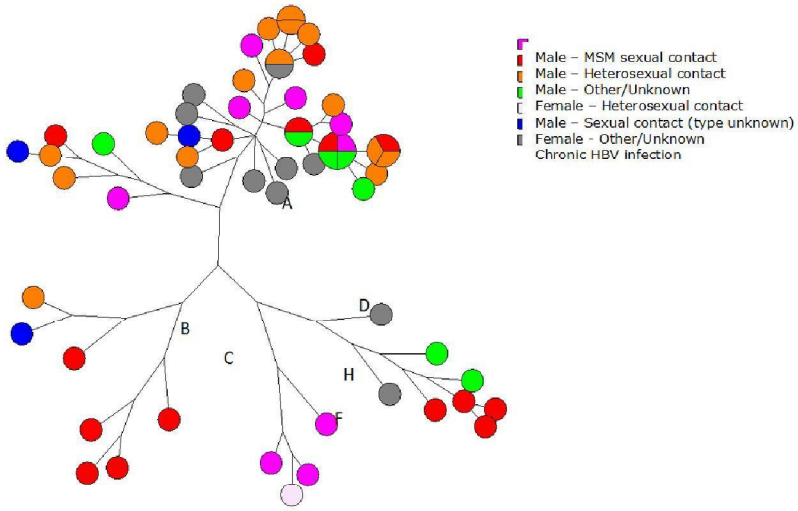
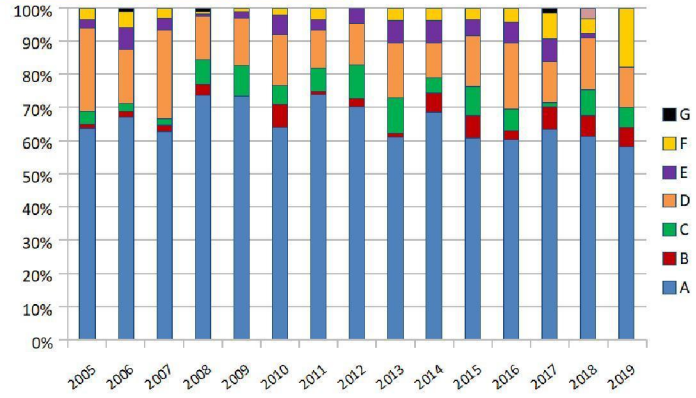


Figure 7.3.2 Optimised maximum parsimony tree based on the full length sequence of HBV cases in the Netherlands in 2018 by reported transmission route (n=60). gX: genotype

Alternatieve figuur over genotypering:



7.3.3 *Epidemiology*

In 2019, 1205 cases of hepatitis B virus (HBV) infection were notified. Of these, 1079 (91%) were chronic infections and 104 (9%) acute infections (22 cases unknown status).

7.3.3.1 Acute HBV epidemiology

The number of notified acute HBV infections was similar in 2019 compared to 2018. In the first half of 2020, 38 cases of acute HBV were reported. The incidence of acute HBV notifications in 2019 was 0.6 per 100,000 population, 0.9/100,000 among men and 0.3/100,000 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). The mean age of patients with acute HBV infection was 44.5 years and is higher in men (48.0) than in women (35.0). The age distribution of acute HBV infection by gender over time is shown in Figure 7.3.2. No cases of acute hepatitis B were reported among children; the youngest patient was 18 years old.

In the period September 2019 to January 2020 three patients died after a fulminant acute HBV infection. Since no mortality due to acute HBV infection was reported in the period 2013-2018 these three cases in a relatively short period are unusual. There was no indication of a common source as the patients were not epidemiologically or phylogenetically linked.

In 2019, most cases of acute HBV infection (58%) were acquired through sexual contact. For 33% 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 for men (38%) than women (18%). Among men (76 cases), sexual contacts between MSM accounted for 20% of acute infections, and heterosexual transmission for 26%. Among women (28 cases), heterosexual contact accounted for 75% of cases. The majority of patients with acute hepatitis B were born in the Netherlands (75%).

7.3.3.2 Chronic HBV epidemiology

The number of chronic HBV notifications is around 1,000-1,100 per year since 2014 (incidence 5.8-6.4 per 100,000) (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 2019, 89% of the chronic HBV patients where the country of birth was known were born abroad. The number of newly diagnosed chronic HBV infections in people born abroad is about 60 times higher than that of people born in the Netherlands (43 compared to 0.8 per 100,000 population. The number of notifications per country of birth fluctuates over time. In 2019 the most frequently reported countries of birth were China (n=99, 11%), Turkey (n=93, 10%) and Poland (n=48, 5%). Around 40 cases each where born in Eritrea, Ghana, Nigeria and Syria. 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).

In 2019, one case of perinatally acquired chronic HBV infection was diagnosed in a child born in the Netherlands in 2017. The child had

received more than three doses of vaccine but it was not reported whether immunoglobulin had been given at birth.

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 2019, samples were available for molecular typing of 74 acute HBV cases (71%) and 23 chronic HBV cases (2%). PCR amplification and sequencing gave results for 66(?) 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 2019, 6 different genotypes were found (Genotype A-F). 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, 58% were genotype A. Genotype D used to be the second most detected genotype among acute cases, but in 2019 genotype F was more frequent (n=12, 18%) than genotype D (n=8, 12%). Genotype A was also most common among chronic cases in risk groups (9/22; 41%), followed by genotype D and E (both 3/22; 14%).

7.3.5 *Research*

7.3.5.1 Hepatitis B revaccination of non-responders

In a Dutch trial almost 500 healthy adults that were non-responders after a primary series of either HBVaxPro-10 or Engerix-B 20, were randomised to receive a second series of three doses of the same vaccine as control, or of Twinrix 20, Fendrix 20, or HBVaxPro 40. Three months after revaccination 67% of the control group had responded, compared to 80% in the Twinrix group, 83% in the HBVaxPro group and 97% in the Fendrix group. As the percentage responders compared to the control group was superior for the last two vaccines it was concluded that the indication for Fendrix and HBVaxPro-40 should be expanded to enable revaccination of non-responders [1].

7.3.6 *Literature*

1.* Raven SFH, (10)(2e), Vossen (10)(2e) LG, Hautvast JLA, Roukens AHE, et al. Serological response to three alternative series of hepatitis B revaccination (Fendrix, Twinrix, and HBVaxPro-40) in healthy non-responders: a multicentre, open-label, randomised, controlled, superiority trial. Lancet Infect Dis. 2020;20(1):92-101.

* RIVM publication

7.4 Human papillomavirus (HPV)

J. Hoes, T.M. Schurink-van 't Klooster, A.J. King, K. van Eer, H. Pasmans, B.H.B. van Benthem, A.W.M. Suijkerbuijk, J.A. Bogaards, F.R.M. van der Klis, H.E. de Melker

7.4.1 *Key points*

- High vaccine effectiveness (VE) against vaccine types HPV16/18 was found for persistent cervicovaginal infections up to nine years post-vaccination.
- Following vaccination with a two-dose schedule high seroprevalence and antibody levels against vaccine-types HPV16/18 up to 72 months of follow-up.
- Vaccinated women 12-24 years of age had a lower risk for a positive hrHPV test in the cervical smear, ASC-US or worse and (H)SIL or worse than unvaccinated women of the same age.
- Bivalent HPV vaccination provides partial protection against GW, especially when administered in early adolescence.

7.4.2 *Tables and figures*

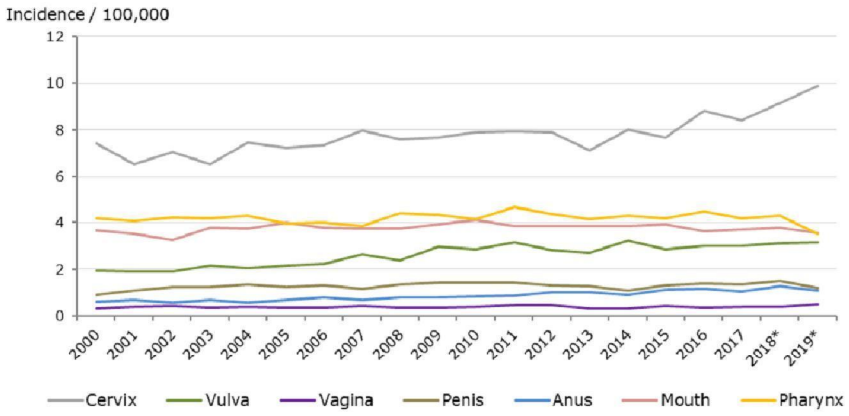


Figure 7.4.1 Incidence / 100,000 (standardised by the European standardised rate) of new cervical, anogenital, mouth/oral and pharynx/pharyngeal cancer cases in the Netherlands in the 2000-2019 period, by cancer type
* Preliminary figures
Source: the Netherlands Cancer Registry (NKR)

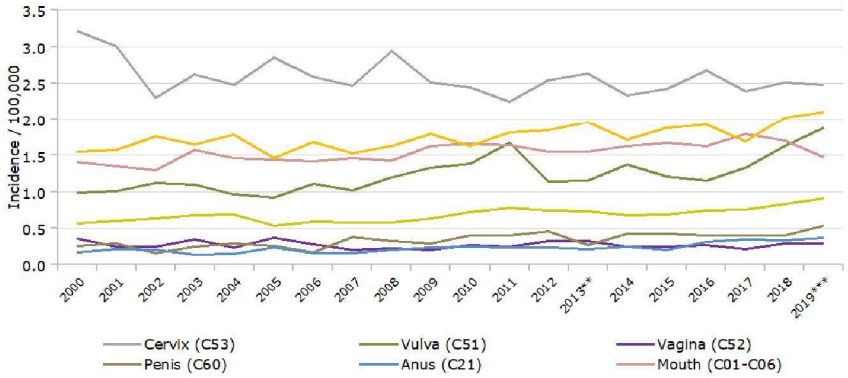


Figure 7.4.2 Incidence / 100,000 of deaths related to cervical, anogenital, mouth, oropharynx and pharynx cancer cases in the Netherlands in the 2000-2019 period, by cancer type

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

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

*** Preliminary figures

Source: CBS

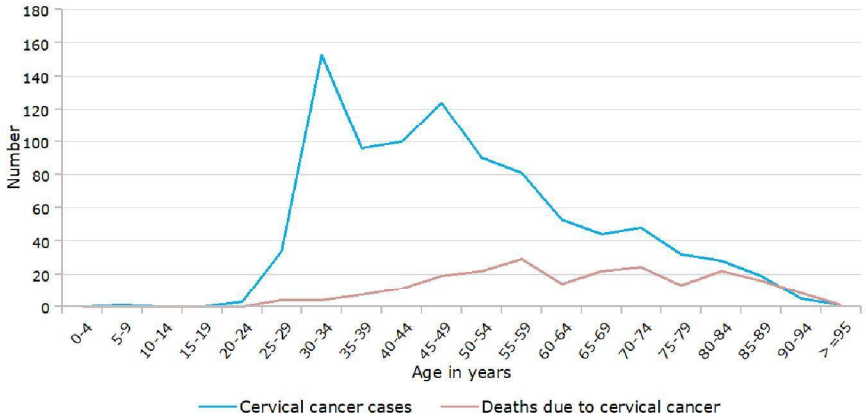


*Figure 7.4.3 Age-specific number of cervical cancer cases and deaths due to cervical cancer in the Netherlands in 2019**

* Preliminary data

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

Incident infections	Adjusted *VE (95% CI)
Vaccine types (HPV16/18)	78.5% (68.4-85.4%)
Cross protective types (HPV31/45)	62.6% (45.5-74.4%)
Cross protective types (HPV31/33/45)	49.9% (32.1-63.0%)
Vaccine and cross protectives types (HPV16/18/31/45)	68.2% (58.3-75.8%)
hrHPV types	14.3% (3.1-24.1%)
Types 9valent vaccine (HPV6/11/16/18/31/33/45/52/58)	32.6% (21.3-42.2%)
Persistent infections (12 months)	**Adjusted* VE (95% CI)**
Vaccine types (HPV16/18)	95.8% (86.6-98.7%)
Cross protective types (HPV31/45)	82.6% (60.8-92.3%)
Cross protective types (HPV31/33/45)	65.0% (38.5-80.1%)
Vaccine and cross protectives types (HPV16/18/31/45)	89.6% (79.8-94.6%)
hrHPV types	22.4% (6.0-35.9%)
Types 9valent vaccine (HPV6/11/16/18/31/33/45/52/58)	49.3% (34.0-61.1%)

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

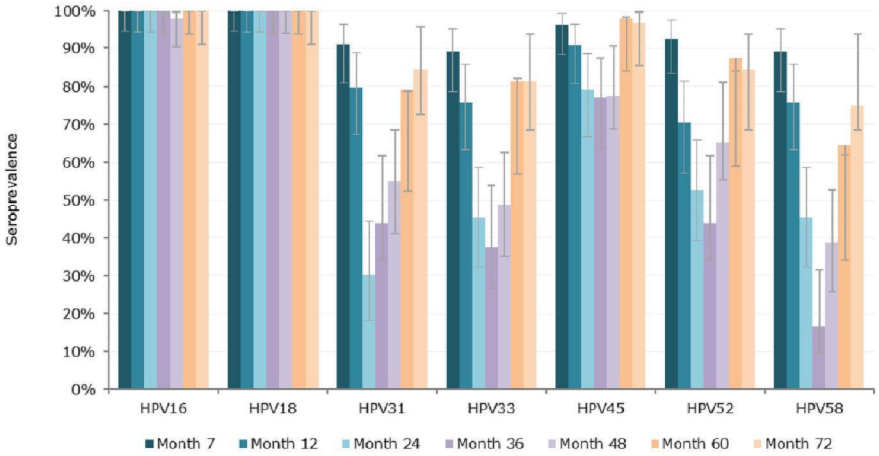


Figure 7.4.4. Seroprevalence among HPV2D participants of HPV types 16/18/31/33/45/52/58 following a two-dose schedule (0, 6 months) at 7, 12, 24, 36, 48, 60 and 72 months after the first dose

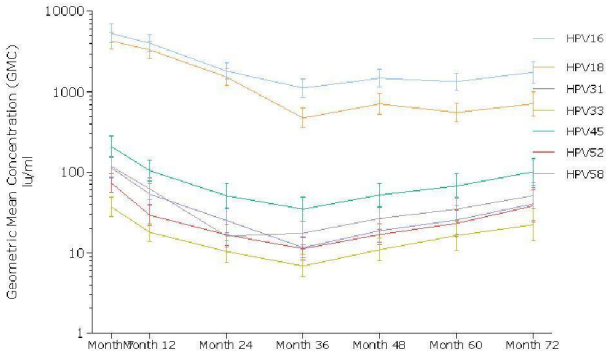


Figure 7.4.5. Geometric Mean Concentrations (GMC; IU/ml) among HPV2D participants of HPV types 16/18/31/33/45/52/58 following a two-dose schedule (0, 6 months) at 7, 12, 24, 36, 48, 60 and 72 months after the first dose

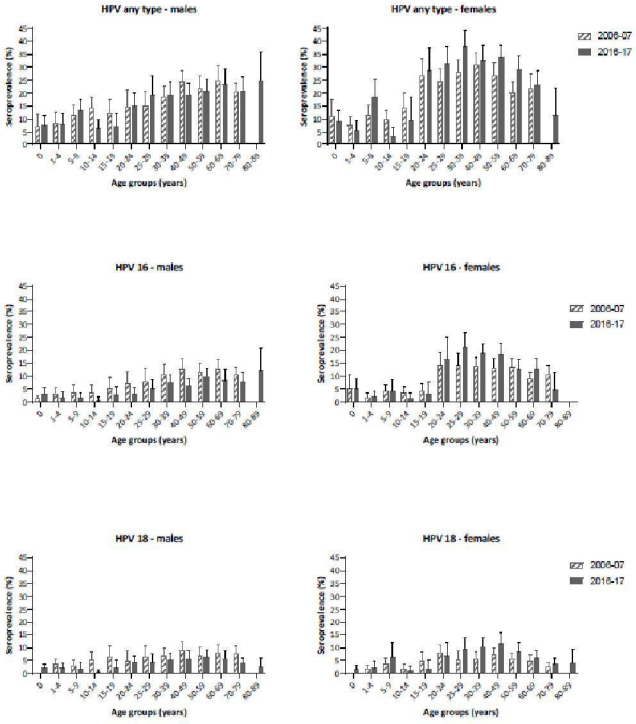


Figure 7.4.6 Seroprevalence of any HPV type (including HPV16/18/31/33/45/52/58), HPV16, and HPV18 in Pienter2 (2006-2007) and Pienter3 (2016-2017) stratified for gender and age group

Table 7.4.2 Association between bivalent HPV vaccination and AGW diagnosed by GPs

Vaccination status	N[a]	Observation time in years	AGW diagnoses	aIRR[b] (95%CI)	aIRR[c] (95%CI)
Unvaccinated	66,487	144,129	296	Reference	Reference
Vaccinated (≥1 dose)	58,299	180,497	310	0.76 (0.65 - 0.89)	0.75 (0.64 - 0.88)
Unvaccinated	66,487	144,129	296	Reference	Reference
Partially vaccinated[d]	31,790	26,409	42	1.15 (0.82 - 1.57)	0.96 (0.68 - 1.32)
Fully vaccinated[d]	53,389	154,088	268	0.72 (0.61 - 0.85)	0.72 (0.61 - 0.86)

Abbreviations: 95%CI: 95% confidence interval; AGW: anogenital warts; aIRR: adjusted incidence rate ratio; GP: general practitioner.
a Number of women that contributed observation time per vaccination status. One woman could contribute observation time to more than one vaccination status. Women with missing educational level were excluded.
b Adjusted for age as time-varying.
c Adjusted for age as time-varying, migration background, educational level, fear of STI/HIV consultations, mean number of GP consultations per years.
d Partially vaccinated: 1 dose or 2 doses <5 months apart. Fully vaccinated: 3 doses or 2 doses ≥5 months apart.

7.4.3 Epidemiology

Human papillomaviruses (HPVs) are a group of DNA viruses infecting cutaneous and mucosal epithelia throughout the human body. Over 200 different HPV types based on DNA sequencing have been identified to date, which differ from each other by at least 10% in the highly conserved L1 gene sequence. A persistent infection with a high-risk HPV (hrHPV) type can lead to the development of (pre-)cancerous lesions at different anogenital and oropharyngeal sites. Thirteen types of HPV are currently considered to be hrHPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). Virtually all cervical cancers are caused by HPV infections. Globally, this led to an estimated 311,000 deaths in 2018, mostly affecting middle-aged women [1]. HPV can also cause vaginal, vulvar, penile, anal, mouth/oral and oropharyngeal cancer. The

relative contribution of hrHPV16 and HPV18 is around 70% to all HPV

-attributable cancers, making them important vaccine targets.

The incidence of cervical cancer in the Netherlands is increasing over the last years to 9.90 per 100,000 in 2019 (preliminary data) (Figure 7.4.1). The number of deaths due to cervical cancer remained relatively stable in 2019 with 2.48 deaths per 100,000 (preliminary data), compared with 2.51 per 100,000 in 2018 (Figure 7.4.2). Incidences and deaths related to other HPV-associated cancers in the Netherlands have remained stable over the last five years (Figure 7.4.1 and Figure 7.4.2). Annually in the Netherlands, approximately 600-850 women are diagnosed with cervical cancer and around 200 women die due to the disease. The age-specific number of cervical cancer cases and deaths caused by cervical cancer in the Netherlands is shown in Figure 7.4.3.

The non-oncogenic, low-risk HPV (lrHPV) types 6 and 11 can cause genital warts (GW). In 2019, the number of GW diagnoses at sexual health centres (SHC) was 928 [2]. The number of diagnoses of GW by GPs was estimated at 44,700 in 2018, which was comparable to figures for the past three years.

7.4.4 Current/ongoing research

7.4.4.1 Whole genome sequencing analysis of HPV16 and HPV18

Whole genome sequence studies on HPV16 and HPV18 positive genital swabs taken from unvaccinated young women in the Netherlands revealed a high degree of host-unique HPV16/18 variants. Conversely, women with a persistent HPV16/18 infection maintained strong conservation of the consensus variant sequence [3, 4]. In vaccinated women, HPV16/18 DNA is also detected sporadically albeit in very low amounts (i.e. the viral load is generally low). Low HPV16/18 viral loads in vaccinated women pose a challenge for whole genome sequencing. To date primarily partial sequences of HPV16/18 genomes (NCR region and E6) isolated from vaccinated women are available. Based on these preliminary results HPV16/18 detected in vaccinated women do not cluster differently from HPV16/18 found in non-vaccinated women. With the improvement of sample processing techniques and deep sequencing, generating whole genome HPV sequences from vaccinated individuals will hopefully be successful in the (near) future.

7.4.4.2 HPV amongst vaccinated and unvaccinated adolescents (HAVANA)

A prospective cohort study (HAVANA) which was initiated in 2009 among vaccinated and unvaccinated 14- to 16-year-old girls, eligible for the catch-up campaign, is still ongoing. The primary aim of this study is to monitor the effect of the bivalent HPV vaccination on HPV-type specific presence amongst 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 showed a significantly high VE against both incident and 12-month persisting vaccine type infections (HPV16/18) up to nine years post-vaccination. High VE against cross protective types was observed (HPV31/45) as well. Pooled VE estimates up to nine years post-vaccination against incident and persistent infections are shown in Table 7.4.1. Type-specific statistically significant VE up to nine years post-vaccination against 12-month persistent infection was found for: HPV16 (94.4%, 95%CI 81.8-98.3%); HPV18 (100%, model did not converge due to absence of infections among vaccinated); HPV31 (85.3%, 95%CI 62.0-94.3%); HPV45 (80.4%, 95%CI 7.5-95.8%). Statistically significant VE estimates against incident infections were found for the same HPV types and HPV35.

In 2016, a second prospective cohort study (HAVANA2) was started among vaccinated and unvaccinated girls (birth cohort 2001). These girls were the first who were eligible for the two-dose HPV vaccination schedule, which initiated in 2014. Follow-up of this cohort is done yearly for at least five years in which girls are asked to fill out a questionnaire

and hand in a vaginal self-swab. For the first round of this study, 39,261 girls were invited for participation. After three years of follow-up (FU), data of 2476 girls could be used of whom 53.1% was vaccinated. Although the absolute number of HPV infections was still low, preliminary vaccine effectiveness against incident infections could be estimated. This resulted in a VE of 82.6% (95% CI 19.9-96.2%) against incident HPV16/18 infections and of 82.4% (95% CI 18.1-96.2%) against HPV31/45 infections. This indicates that the two-dose schedule provides high protection in a population-setting against both vaccine and cross protective HPV types up to four years post-vaccination.

7.4.4.3 Performance of HPV detection of HPV type 59 and HPV type 45 with the SPF10 system

The broad spectrum L1-based SPF10-DEIA LIPA25 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 HPV45 and HPV59 infections. We investigated the HPV45 and HPV59 detection sensitivity of the SPF10 system and compared it to detection with type specific HPV45- and HPV59 qPCR assays. Missed HPV45 and HPV59 infections had significant lower viral loads compared to detected HPV45 and HPV59. Preliminary data suggest that HPV59 infections in non-vaccinated participants were missed more frequently with the SPF10 detection system. Interestingly, HPV59 detection seemed more hampered by the presence of co-occurring HPV types compared to HPV45. SPF10 detection of HPV59 was likely most hampered in non-vaccinated individuals, as they often carry more HPV types. As a result, a great impact on vaccine effectivity (VE) estimates for HPV59 was observed based on the SPF10 method (strong negative) and the TS qPCR assay (no apparent VE effect), while this change was not observed for HPV45.

7.4.4.4 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. Annually, girls donate a blood sample and fill in questionnaire. To date results were available up to the sixth year. These results showed high seroprevalence and antibody levels against vaccine-types HPV16/18 up to 72 months of follow-up (Figure 7.4.4 and Figure 7.4.5). Waning in antibody levels was seen up to 36 months, thereafter the levels remained stable (Figure 7.4.5). Seroprevalence and antibody levels were considerably lower for HPV types 31, 33, 45, 52, 58 (Figure 7.4.4 and Figure 7.4.5).

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

The PASSYON study is a biennial cross-sectional survey conducted among 16- to 24-year-old visitors of sexual health centers in the Netherlands [5]. We used data from MSM included in PASSYON study years 2009-2017. MSM provided a penile and anal swab for HPV DNA testing and blood for HPV antibody testing. There were no significant declines in the HPV prevalence among MSM up to eight years after introduction of girls-only HPV16/18 vaccination, indicating that MSM are

unlikely to benefit largely from herd effects from girls-only vaccination. Most MSM were vaccine-type DNA negative and seronegative, suggesting that vaccination of young MSM visiting SHCs could still be beneficial [6].

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

Using data from the PASSYON study from 2009-2017, we studied trends in the prevalence of 25 HPV types (including vaccine types) following the introduction of HPV vaccination in the Netherlands in 2009. Among all women, heterosexual men, and unvaccinated women a yearly percentual decline was observed for HPV16/18 ranging from 13% for all women and heterosexual men, to 5.4% for unvaccinated women. Additionally, we observed significant declines in HPV31 (all women and heterosexual men), HPV45 (all women), and in all high-risk HPV types pooled (all women and heterosexual men). Significant increases were observed for HPV56 (all women) and HPV52 (unvaccinated women). These results indicate both first and second order herd effects against vaccine types from girls-only vaccination up to 8 years post vaccination implementation. Moreover, heterosexual men also benefit from herd effects against cross protective types. These results are promising regarding population-level and clinical impact of girls-only HPV16/18 vaccination in a country with moderate vaccine uptake.

7.4.4.7 Genital warts in GP sentinel surveillance (NIVEL)

There is ongoing debate about the possible protective effect of the bivalent human papillomavirus (2vHPV) vaccine, targeting oncogenic types HPV16/18, against anogenital warts (AGW), commonly attributed to HPV6/11. We performed a retrospective registry-based open cohort study to assess the effect of 2vHPV vaccination on AGW. We linked general practitioners (GPs) data from women born between 1993-2002, who had been eligible for HPV vaccination in the Netherlands, to the Dutch national immunization registry on an individual level. Women were followed until their first AGW diagnosis or end of follow-up. We linked data of 96,468 women with in total 328,019 years observation time and 613 AGW diagnoses (incidence: 1.87/1,000 person-years). The AGW incidence was lower among those with ≥1 dose versus 0 doses (adjusted incidence rate ratio 0.75, 95% confidence interval (CI) 0.64-0.88) (Table 7.4.2). This is the largest population-based study so far to examine the effect of 2vHPV vaccination on AGW, with reliable individual information on AGW diagnoses and vaccination status. The results indicate that 2vHPV vaccination partially protects against AGW, especially when administered in early adolescence [7].

7.4.4.8 Trend analysis of cytological abnormalities in opportunistic cervical screening among young women in the Netherlands

HPV-vaccine eligible girls will enter the Dutch cervical screening program at 30 years of age, i.e. from 2023 onwards. However, it appears that every year a substantial number of young women before the age of 30 have a cervical smear test taken outside the regular screening program. In this study we used data of opportunistic screening to explore trends in cytological abnormalities and to indicate possible early effects of HPV vaccination. Therefore, women with a cervical smear test before than 30 years of age between 1995 and 2016 from the nationwide network and

registry of histo- and cytopathology in the Netherlands (PALGA) were analyzed. Annually, on average 42,500 (range 29,419 to 105,812) girls younger than 30 years of age (0.025% of the population) had a cervical smear test taken between 2000 and 2016. The percentage of atypical squamous cells of undetermined significance (ASC-US) is increasing since 2001. The percentage also increases with age up to the age of 24 and thereafter declines again. The percentage of high-grade squamous intraepithelial lesions ((H)SIL) remained stable up to 2006 but increased thereafter. The percentage of (H)SIL increases steadily with age. The increasing trend has not been halted by HPV vaccination yet, which is likely due to the rather young age of vaccine-eligible girls in the study period (i.e. up to 23 years of age) and the suboptimal vaccination coverage in the Netherlands (46-61%).

7.4.4.9 Effect of HPV vaccination on cervical lesions in opportunistic screening among young women in the Netherlands

In 2023 the first girls who were eligible for HPV-vaccination, will enter the cervical screening program. However, a substantial number of young women have a cervical smear test taken before the start of the regular screening program. This study was initiated to explore possible early effects of HPV-vaccination on cervical lesions in opportunistic screening. In this study, cytology results of cervical smear tests from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) were linked to the women's HPV-vaccination status from the national vaccination registry (Praeventis). The cohort consists of girls eligible for HPV-vaccination (i.e. born from 1993 onwards) who have had a cervical smear test taken between 2009 and March 2018. A total of 42,214 young women did have one or more cervical smear tests during the study period. Percentages of vaccination coverage among these young women were comparable with the national vaccination coverage (45-61%). Results of logistic regression analysis showed that fully vaccinated women 12-24 years of age had a lower risk for hrHPV (OR corrected for age and birth cohort: 0.68; 95%CI 0.62-0.74), ASC-US or worse (OR: 0.77; 95%CI 0.73-0.82) and (H)SIL or worse (OR: 0.45; 0.37-0.56) than unvaccinated women of the same age. In incompletely vaccinated girls a smaller effect was seen than in fully vaccinated girls, i.e. for hrHPV 0.75 (0.61-0.93) for ASC-US or worse 0.96 (0.86-1.08) and for (H)SIL or worse 0.60 (0.38-0.96). So, by linking nation-wide registries on cytopathology and vaccination, we were able to show significant early effects of HPV-vaccination on cervical lesions in young women even before the start of the cervical screening program.

7.4.4.10 Determinants of HPV-vaccination uptake over time in the Netherlands

This study was initiated to gain insight into the relationship between social, economic, cultural and political factors and the vaccination rate and whether the influence of these factors changed over time. Results showed that having not received a MMR-vaccination, having one or two parents born in Morocco, Turkey or two parents born in the Netherlands Antilles and Aruba, a lower socioeconomic status, higher urbanization level, higher road distance and higher voting proportions in municipalities for Christian political parties and populist parties with liberal-conservative views were associated with a lower HPV-vaccination uptake. Besides some changes in political preferences of the population

we found no clear determinants which could possibly explain the decrease in the HPV-vaccination uptake.

7.4.4.11 HPV seroprevalence in the Netherlands (Pienter studies)

As the bivalent HPV-vaccination was included in the National Immunization Program in the Netherlands, we examined the possible changes in HPV-seroprevalence in the HPV unvaccinated Dutch population aged 0-89 years by comparing pre-vaccination data with data of approximately six years post-implementation of national vaccination. We therefore made use of the Pienter studies, were we collected serum samples of men and women, performed before (2006-07, n=6384) and after (2016-17, n=5645) implementation of HPV-vaccination in the Netherlands. Seven high-risk HPV-specific antibodies (HPV16, 18, 31, 33, 45, 52, and 58) were tested in a virus-like-particle-based multiplex-immunoassay. Type-specific HPV-seroprevalence had increased in women between 2006-07 and 2016-17. Also, a higher seroprevalence for at least one type in women >15 years was found in 2016-17 (31.7%) compared with 2006-07 (25.2%). In men, overall HPV seroprevalence remained similar, however a lower seroprevalence was found for HPV16 in 2016-17 (7.5%) compared with 2006-07 (10.6%). These results indicate an increase in exposure of high-risk HPV types in women and a rather stable exposure in men. No clear effects of the strategy of girls-only vaccination were observed in men, probably because of the short time after introduction combined with suboptimal vaccination coverage.

7.4.4.12 HPV seroprevalence on the BES-islands

Incidence and mortality of human papillomavirus (HPV)-related cancers differs geographically, with high rates in Caribbean countries. Seroepidemiological data could therefore provide information on lifetime cumulative HPV exposure and contributing risk factors, but this has not been available yet for Caribbean Netherlands (CN), comprising the islands Bonaire, St. Eustatius and Saba. Therefore, a cross-sectional population-based serosurveillance study was performed in this (recently girls-only HPV-vaccinated) population in 2017. Blood samples from participants (n=1,823, 0-90 years) were tested for seven high-risk (hr)-HPV-specific IgG-antibodies using a VLP-based multiplex-immunoassay. We found that among individuals aged ≥15 years, overall seropositivity was high (34.0%), with over half of them being seropositive for ≥2 hr-HPV types, and HPV16 and 52 being most prevalent (13%). Seroprevalence was substantial higher in women (51%) than men (18%), predominantly peaking in women aged 20-59 years, and was highest on St. Eustatius (38%). In accordance with the Caribbean region, seroprevalence of multiple hr-HPV types was high in CN. These data corroborate the decision regarding introduction of a sex-neutral HPV-vaccination program and the relevance for considering a population-based cervical cancer screening program [8].

7.4.4.13 Modelling

In May 2018, the Director-General of the WHO made a global call for action aiming to eliminate cervical cancer. This initiative is currently

investigating which approaches can accomplish this mission within the 21st century. Two recent studies assessing the health impact of girls' HPV vaccination strategies, found that it would require at least 90% uptake in girls to achieve the WHO target levels for the near-elimination of cervical cancer incidence and mortality in many low- and middle-income countries [9, 10]. Previous modelling studies have suggested that the same holds for high-income countries. However, such consistent high coverage is hard to achieve and elimination of oncogenic HPV types might already be achieved with moderate vaccination coverage if a sex-neutral strategy is applied [11]. Moreover, the population impact will depend on the HPV vaccine type and the specific vaccination strategy in place [12], as well as on the still unresolved possibility of type replacement [13].

A recent modelling study, based on a Finnish community-randomized trial comparing sex-neutral as well as girls-only HPV16/18 vaccination to a control (hepatitis B-virus vaccination) arm, predicted that 75% coverage in a sex-neutral program could suffice to eliminate vaccine types HPV16/18 as well as cross-protective types HPV31/33 [14]. Therefore, the authors claim that sex-neutral vaccination is "superior for eradication of oncogenic HPVs" [14]. Note, however, that 75% coverage in both sexes constitutes a higher absolute vaccine administration than full coverage in a single-sex program [11].

7.4.5 International developments

Following the call from the WHO Director General in 2018, a Draft Strategy for the elimination of cervical cancer as a public health problem was put for the World Health Assembly's approval in May 2020 [15]. The Draft Global Strategy outlines that cervical cancer is eliminated as a public health problem when all countries reach an incidence rate of less than 4 cases per 100,000 women. To reach elimination, efforts must be aligned and accelerated. Every country must reach the following global targets by 2030:

- 90% coverage of HPV vaccination of girls (by 15 years of age);
- 70% coverage of screening (70% of women are screened with high-performance tests by the ages of 35 and 45 years) and 90% treatment of precancerous lesions;
- Management of 90% of invasive cancer cases.

7.4.5.1 Impact of HPV vaccination

In a community-randomized trial from Finland, vaccine effectiveness of the HPV16/18 vaccine against oropharyngeal HPV infections could be determined. This study showed VE estimates up to 6 years post-vaccination among females aged 18,5 years. Highest effectiveness was observed against HPV16/18 infections, (82.4% (95% confidence intervals [CI]: 47.3–94.1), while VE was 69.9% (95% CI: 29.6–87.1) for

HPV 31/33/45 infections. This indicates the AS04-HPV-16/18 vaccine is

effective against oropharyngeal HPV infections and could aid in the reduction of head- and neck-cancers [16].

The incidence of vulvar pre-cancer and cancer was examined in Denmark over the 1997–2018 period. Age-standardized and age specific incidence rates of vulvar squamous cell carcinoma (VSCC) and precancerous lesions were expressed using the average annual percentage change (AAPC). The age-standardized incidence rate of VSCC showed an average yearly increase of 2.95% (95%CI: 2.15–3.75) in the study period, like the incidence of vulvar precancerous lesions (AAPC = 2.38%; 95%CI: 1.75–3.02). After implementation of HPV vaccination, the incidence of vulvar precancerous lesions decreased significantly in women aged <20 years (AAPC =−22.10% (95%CI: −35.27 to −6.26)) and 20–29 years (AAPC=−6.57, 95% CI: −10.63 to −2.33), whereas the incidence increased in most age groups ≥50 years. This indicates that, although overall incidence of vulvar (pre-) cancer was increasing, a possible positive effect of HPV vaccination was observed in vaccine-eligible age groups [17].

In order to obtain insight into the range of the cross-protective effect of the bivalent HPV vaccine, pooled efficacy estimates based on individual-level data from two randomized controlled trials were established against incident HPV infections and cervical abnormalities. Statistically significant efficacy was observed for individual oncogenic types 16/18/31/33/45/52 and nononcogenic types 6/11/53/74 6-month persisting infections. Efficacy against cervical abnormalities (caused by all HPV types) increased with severity, ranging from 27.7% (95% CI 21.7% to 33.3%) to 58.7% (95% CI 34.1% to 74.7%) for cytologic outcomes and 66.0% (95% CI 54.4% to 74.9%) to 87.8% (95% CI 71.1% to 95.7%) for histologic outcomes (CIN2+ and CIN3+, respectively). This indicates that bivalent HPV vaccination probably provides some additional cross protection besides established types, which could lead to higher efficacy against clinical outcomes [18].

A head-to-head comparison was made regarding GW incidence rates (IRs) in Norway and Denmark following quadrivalent HPV vaccination. Both countries started routine vaccination for 12-year-old girls in 2009, but Denmark additionally offered vaccination for older age groups. HPV vaccination coverage among women aged 12–35 years in 2015 was 24% in Norway and 70% in Denmark. GWs IRs in Norway and Denmark decreased annually in 2009–2015 among women by 4.8% (95% confidence interval: 4.3 to 5.3) and 18.0% (95%CI: 17.5 to 18.6), respectively, and among men by 1.9% (95%CI: 1.4 to 2.4) and 10.7% (95%CI: 10.3 to 11.2), respectively. This indicates that vaccination catch-up campaigns can aid in fast(er) declines of HPV related morbidity, both in women and in unvaccinated men. However, high vaccine uptake is important to accomplish this [19].

Potential human papillomavirus (HPV) vaccination and cervical screening scenarios in low-income and lower-middle-income countries (LMICs) were modelled to examine the feasibility and timing of elimination of cervical cancer. Three base-case scenarios were compared: girls-only vaccination, girls-only vaccination and once-lifetime screening, and girls-only vaccination and twice-lifetime screening. Different elimination thresholds were studied: an average age-standardized cervical cancer incidence of four or fewer cases per 100 000 women-years, ten or fewer

cases per 100 000 women-years, or an 85% or greater reduction in incidence. Girls-only HPV vaccination was predicted to reduce the median age-standardized cervical cancer incidence in LMICs from 19.8 (range 19.4–19.8) to 2.1 (2.0–2.6) cases per 100 000 women-years over the next century (89.4% [86.2–90.1] reduction). Adding twice-lifetime screening reduced the incidence to 0.7 (0.6–1.6) cases per 100 000 women-years (96.7% [91.3–96.7] reduction). Girls-only vaccination was predicted to result in elimination in 60% (58–65) of LMICs based on the threshold of four or fewer cases per 100 000 women-years, in 99% (89–100) of LMICs based on the threshold of ten or fewer cases per 100 000 women-years, and in 87% (37–99) of LMICs based on the 85% or greater reduction threshold. When adding twice-lifetime screening, 100% (71–100) of LMICs reached elimination for all three thresholds. This indicates that high HPV vaccination uptake can lead to the elimination of cervical cancer in most LMCI's. This is endorsed as an important public health goal by the WHO [9].

7.4.5.2 Reduced dosing schedule

A two-dose schedule is currently the most often used in national immunization programs worldwide. However, since a few years attention has arose for a one-dose HPV vaccine schedule. In several studies one dose recipients showed robust and sustained antibody levels against HPV16 and HPV18 over a nine-year period. Although being inferior to two- and three dose vaccinated girls, frequencies of incident and persistent HPV16 and HPV18 infections were similar and uniformly low in all the different doses groups up to 7 years of follow-up [20-22]. Moreover, cellular immunity followed a one-dose schedule was detectable after 6 years [23, 24].

These data suggest that either a single dose of the bivalent or quadrivalent HPV vaccine has comparable effectiveness and is immunogenic, which could give long-lasting protection against infections against HPV-vaccine types. Therefore, a one dose vaccination could be a viable strategy when working towards the global elimination of cervical cancer. Randomized controlled trials with a focus on evaluation on the protection afforded by a single dose of HPV vaccine are now on its way. Results are to be expected in the upcoming years.

7.4.5.3 Cost-effectiveness

Datta et al. assessed the cost-effectiveness of HPV vaccination for both girls and boys in the UK. In an economic model healthcare costs and quality-adjusted life years were assessed using the three HPV vaccines currently available, vaccinating either girls alone or both sexes. Vaccinating girls is extremely cost-effective compared with no vaccination, vaccinating both sexes is less so. Adding boys to an already successful girls-only programme has a low cost-effectiveness, as males have high protection through herd immunity. The generic conclusion from this work is that as coverage in girls increases, there is less incremental benefit from adding boys to the programme, due to existing herd immunity. In the case of the UK, with a high reported sustained HPV vaccine uptake rates in girls, it is unlikely that adding boys will be cost-effective within standard economic guidelines which assume a 3.5% economic discounting. However, given the long time-scales associated

with HPV infection and resulting disease, it may be more appropriate to adopt a 1.5% discounting, as is used in the Netherlands, in which case adding boys to the programme becomes cost-effective for all three vaccines considered [25].

In the United States, the routine age for HPV vaccination is 11 to 12 years, with catch-up vaccination through age 26 years for women and 21 years for men. U.S. vaccination policy on use of the 9-valent HPV vaccine in adult women and men is being reviewed. Laprise et al. evaluated the cost-effectiveness of extending the current U.S. The current HPV vaccination program is predicted to be cost saving. Vaccinating women and men up to age 30, 40, and 45 years is predicted to cost $830,000, $1,843,000, and $1,471,000, respectively, per quality-adjusted life-year gained (vs. current vaccination). To conclude, extending vaccination to older ages is predicted to produce small additional health benefits and result in substantially higher incremental cost-effectiveness ratios than the current recommendation [26].

Mahumud et al assessed the cost-effectiveness of adding a nonavalent new Gardasil-9® (9vHPV) vaccine to the national immunization schedule in Australia across three different delivery strategies [27]. The 9vHPV vaccination was estimated to prevent 113 new cases of cervical cancer (discounted) during a 20-year period compared with the quadrivalent 4vHPV vaccine. Considering delivery strategies, the ICERs per DALY averted were A$46,378, A$43,729, and A$43,930 for school, health facilities, and outreach-based vaccination programs from the societal perspective. All estimates of ICERs fell below the threshold level (A$73,267). This cost-effectiveness evaluation suggests that the routine two-dose 9vHPV vaccination strategy of preadolescent girls against HPV is very cost-effective in Australia.

7.4.5.4 Screening uptake

Chua et al. studied the influence of HPV vaccination on high-risk sexual behaviour, and intention for cervical screening among young Chinese females [28]. The study was conducted in secondary schools (in-school) and among community females between 18 and 27 years (out-school). They showed that vaccinated Chinese young females had a higher intention for cervical screening, i.e. 23.6% vs. 21.1% for in-school girls and 53.6% vs. 43.6% for out-school females. Costs and knowledge were important factors for non-vaccination and non-intention for cervical screening.

7.4.5.5 Male vaccination

In light of the global HPV vaccine supply shortage, the WHO Strategic Advisory Group of Experts (SAGE) proposed to temporarily pause implementation of male HPV vaccination programs [29]. The supply shortage is most likely only temporary and, as also mentioned in the 2019 SAGE meeting, it is to the responsibility of 'the vaccine manufacturers to be operationally and ethically responsive to global vaccine supply needs and align with WHO´s call for action for elimination of cervical cancer' [29]. Moreover, countries still need to weigh local vaccine coverage, disease burden, and considerations of (economic) efficiency in order to support local decision making.

To further the discussion on the economic efficiency of sex-neutral HPV vaccination in high-income settings, a systematic account of its incremental cost-effectiveness relative to girls-only vaccination is needed. The majority of studies that evaluated sex-neutral compared to girls-only HPV vaccination concluded that preadolescent male vaccination would not be cost-effective, primarily owing to assumptions of high vaccine uptake among girls and high costs of vaccination [30]. However, in most European countries, vaccine uptake among girls has been lower than anticipated [31], while strong vaccine price reductions have been realized via tendering procedures and adoption of reduced dosing schemes [32].

For this reason, we investigated the cost-effectiveness of sex-neutral HPV vaccination in European settings with information on tender-based vaccine prices, taking actual levels of vaccine coverage into account. A Bayesian synthesis framework for health economic evaluation was applied that accommodated country-specific information on key epidemiologic and economic parameters. To tailor region-specific herd effects, we used projections from three independently developed HPV transmission models. We found that sex-neutral HPV vaccination is economically attractive in all European tender-based settings. Still, tendering mechanisms need to ensure that boys' vaccination will remain cost-effective at high vaccine uptake rates, as sex-neutral vaccination remained cost-effective in 8 out of the 11 countries included at an assumed 80% uptake in both sexes [33].

7.4.6 Literature

7.4.6.1 References

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7.5 Measles

I.K. Veldhuijzen, R. Bodewes, W.L.M. Ruijs, A. Suijkerbuijk, R. van Binnendijk, N.Y. Rots, C.A.C.M. van Els, H.E. de Melker

7.5.3 Key points

- The number of measles cases in 2019 was relatively high with 84 reported cases. In the first six months of 2020 only 2 cases were reported, possibly related to the COVID-19 pandemic.
- From June to August 2019 a local outbreak occurred in a low vaccination municipality with 32 reported cases, mainly among unvaccinated children.
- Genotype D8 was the only genotype detected.
- Results from the 2016/2017 PIENTER study indicate high overall seroprevalence of protective antibodies in 97% of the general population.

7.5.4 Tables and figures

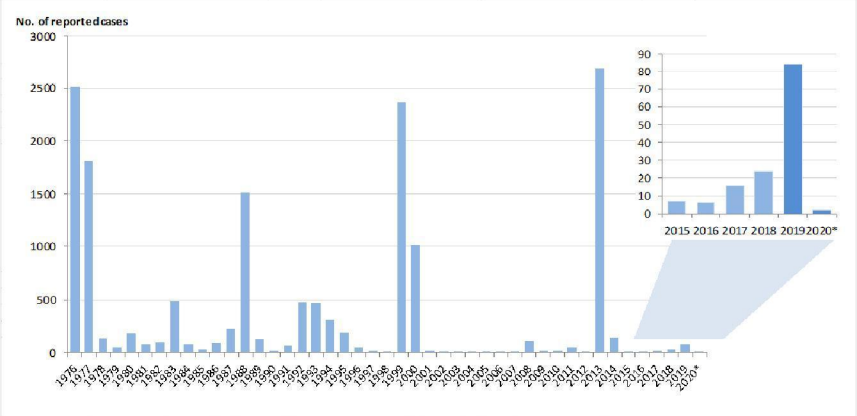

Figure 7.5.1 Annual reported measles cases since the introduction of measles in the Dutch vaccination programme.
* up to July

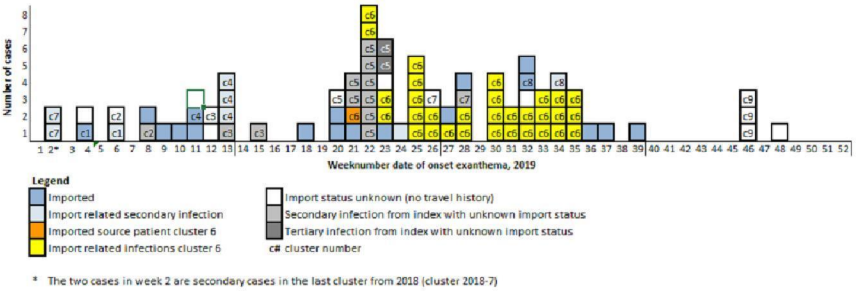

Figure 7.5.2 Epidemic curve of reported measles cases in 2019 by week of onset and import status.

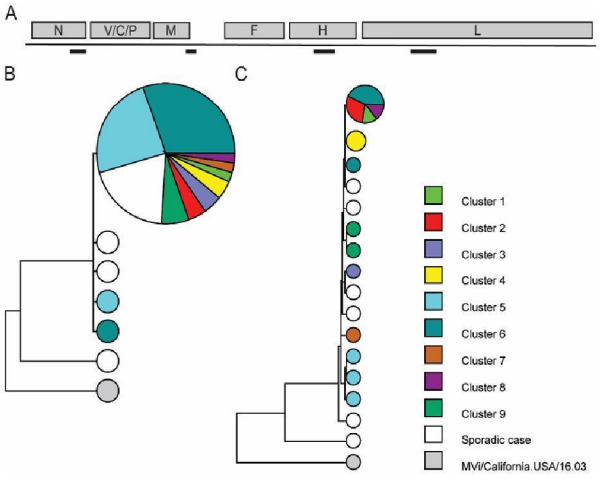

Figure 7.5.3 Analysis of nucleotide sequence data of 23 measles viruses detected in the Netherlands in 2019. A. To increase the molecular resolution, sequence data of multiple parts of the measles virus genome were determined (black bars) in addition to the standard N450 sequence used for genotyping according to the WHO protocol. B, C. Dendograms (prepared with Bionumerics version 7.6.3) provide insights in the nucleotide variation between different viruses based on the N450 sequence data only (B) or all obtained sequence information (C). Viruses with identical nucleotide sequences were grouped together and size of circles displays the number of viruses, while the colour represent the epidemiological cluster or sporadic case.

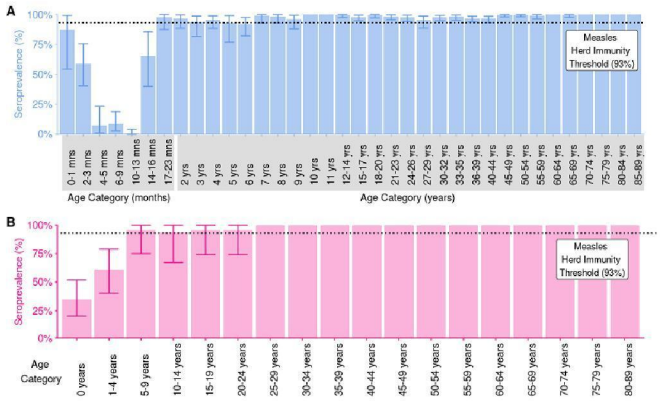

Figure 7.5.4 Seroprevalence of measles IgG antibodies (cut-off is ≥12 IU/ml) by age category in The Netherlands, 2016/17. Panel A: Results for the general Dutch Population (N=5,146); Panel B: Results for the Protestant Orthodox Reformed community (N=1,355).

7.5.5 *Epidemiology*

The number of reported measles cases was 84 in 2019 which was relatively high compared to the previous years and corresponds to an incidence of 0.5 per 100.000 population (Figure 7.5.1). In the first six months of 2020 only two cases were reported, with dates of onset in January and February. The low number of cases in the first half of 2020 could be related to reduced travel and social distancing measures as a result of the COVID-19 pandemic. The mean age of the patients in 2019 was 19 years (range 7 months to 54 years), and 48 (57% were male).

An epidemic curve of the cases in 2019 is shown in Figure 7.5.2. In 2019, 20 cases (24%) were imported with measles acquired in France (n=4), Poland (n=3), Ukraine (n=2), Belgium (n=2) and 9 other countries. Four of these led to onward transmission resulting in 38 import-related infections (45%). For the remaining 26 patients (31%) the import status was unknown as they were infected in the Netherlands from an unknown source or part of a cluster for which the index patient had an unknown source. Overall 69% of the measles cases in 2019 were imported or import related.

In 2019 nine clusters were identified including 61 patients. One cluster in May 2019 occurred in a work setting and included 9 patients born between 1974 and 1980. The largest cluster included 32 patients notified in a municipality with low vaccination coverage between June and August 2019. This number is likely an underestimate of the true number of infections. The cluster consisted mainly of unvaccinated children (91%) and 23 of the 32 patients (72%) were born after 2012 (i.e. just before or after the last epidemic in 2013/2014). The three children who were vaccinated had received MMR0 at the age of 6

months in the previous outbreak, and MMR1 at 14 months of age. The clinical picture in these children was mild.

Of the cases reported in 2019, 52 (68%) were unvaccinated, eight of them were 14 months or younger and therefore too young to be vaccinated. Twenty-five patients (32%) were reportedly vaccinated, although 11 with only one dose. For seven patients the vaccination status was unknown. Fourteen patients were hospitalised, one of them with pneumonia. Five (36%) of the hospitalised patients were vaccinated, three with one dose and two with unknown number of doses.

In the first half of 2020, only two cases were reported, with dates of onset in January and February. The first patient had an unknown vaccination status and got infected with measles virus in Romania. The second patient was an unvaccinated 3 year old who was admitted to the hospital. The source of infection remained unknown for this patient.

7.5.6 *Pathogen*

A genotype was determined of the detected measles virus of 56 (67%) reported cases in 2019 and 2 (100%) reported cases in the first six months of 2020. Measles virus genotype D8 was detected in all cases. Measles virus genotype D8 was in 2019 also the genotype that was most often detected in Europe based on sequence data available in the global Measles Nucleotide Surveillance (MeaNS) database [1, 2].

In 49 out of 56 measles viruses for which a genotype was obtained in 2019, the obtained nucleotide sequence data from measles viruses (450 nucleotides of the nucleoprotein gene) was exactly identical to measles virus D8 named strain MVs/Gir Somnath.IND/42.16 and epidemiological clusters could not be supported with nucleotide sequence data. Therefore, additional sequence information was obtained from a selection of measles viruses. The partial non-coding region between the M and F protein genes, the partial H protein gene and the partial L protein gene (in total 1605 nucleotides) were selected based on relatively high sequence variation between different strains [3]. Use of these data increased the molecular resolution and improved support of epidemiological clustering, although for four epidemiological clusters no sequence variation between detected measles viruses was observed (Figure 7.5.3). To further increase the molecular resolution, analysis of complete measles virus genomes (typically 15894 nucleotides) would be the next step.

7.5.7 *Research*

7.5.7.1 Pienter3

Seroepidemiology is an important tool to monitor the (long term) effects of the national immunization programme. In The Netherlands every ten year a population-based study is performed (1995/1996-2006/2007-2016/2017) to assess the immunity in the Dutch population (0-79/89 years of age) and among orthodox reformed individuals that are socio-geographically clustered and often refuse vaccination. The third study was conducted in 2016-2017 and included over 7000 participants [4]. Serum samples were analysed by a bead-based multiplex immunoassay. For measles, IgG levels of ≥0.12 IU/ml were considered protective.

Preliminary analyses indicate high overall seroprevalence of protective antibodies in the Dutch population of 97% for measles. Antibody concentrations are higher in the naturally infected cohorts compared with vaccinated cohorts. The seroprevalence among the population offered two doses of MMR vaccine, those aged between 10 and 39 years, is high and varies between 96.1% and 100%. Susceptibility was higher among orthodox reformed individuals. Of the orthodox Protestant participants, children born after the last measles epidemic in 2013/2014 often lacked protective antibodies against measles. Age-specific prevalence is presented for both the general population and the orthodox Protestant participants in municipalities with low vaccination coverage in Figure 7.5.4.

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

Children that were at increased risk for 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 [5]. For further long term follow-up the participating children will be asked to collect additional blood sample at age 7.

Also the cellular basis of the acquired measles immunity following early and routine MMR vaccination is currently being investigated in more detail.

7.5.7.3 Humoral and cellular response to natural measles virus infection (Immfact study)

Over the past years longitudinal blood samples were collected for immunological studies from a small cohort of mostly non-related, vaccinated, adult measles cases (n=27) recruited in the 2013-2014 measles outbreak. Studies in unvaccinated children during this outbreak illustrated that full blown measles virus infection induces durable anti-measles immunity but causes immunological 'amnesia' for other pathogens. To investigate this paradox in secondary vaccine failure, serum samples from the Immfact cohort were tested in a multiplex immunoassay (MIA), comparing kinetics of IgG antibodies to measles virus with those to other pathogens. Preliminary results are expected end of 2020. Typing of human leukocyte antigens (HLA) in this cohort of mostly vaccinated adult cases indicated a strongly increased prevalence of an ancestral haplotype. Whether this indicates a role for aberrations in cellular immunity in secondary measles vaccine failure needs to be further explored.

7.5.7.4 Measles among vaccinated people

Several patients in a cluster of measles cases in a work setting in May 2019 were vaccinated. To investigate the cluster in more detail additional serological analysis were performed on samples from the employees with complaints, and a questionnaire was sent to all employees in the company. In total 11 employees with complaints were included in the study. Based on the serological analysis and vaccination history 4 unvaccinated employees were classified as having a naïve infection, 1 once vaccinated person had primary vaccine failure, 4 had a breakthrough infection after vaccination (1 was vaccinated with one dose and 3 with two doses), and 1 had no evidence of being exposed to measles virus. The four patients that were hospitalized had a naïve infection (n=3) or primary vaccine failure (n=1). The patients with breakthrough infection had less severe clinical signs than the other cases. Of employees born in or after 1975, 94% was vaccinated. The

small size of this outbreak was most likely due to the high vaccination coverage among employees. A paper about the cluster investigation is in preparation.

7.5.8 *International developments*

Several reviews on the effect of the age at measles vaccination have been published [6-9]. Two reviews by Nic Lochlainn et al focus at children who receive the first dose of measles containing vaccine (MCV1) below 9 months of age. They report that seroconversion after MCV1 increases with age, and that seropositivity after a second dose is high and did not depend on age of MCV1. However, some evidence suggested that MCV1 below 9 months of age resulted in lower antibody titres after one or two subsequent doses of MCV than when measles vaccination is started at age 9 months or older. Epidemiological data reviewed by Carazo et al comparing one-dose vaccine effectiveness for children vaccinated from 6 to ≥15 months indicated older age improved measles. The review by Hughes et al looked at whether measles vaccine effectiveness (VE) waned over time, and if so, whether this differed between measles-eliminated and measles-endemic settings. In measles-endemic settings, one-dose VE increased by 1.5% for every month increase in age at MCV1, and no evidence of waning VE was found. Only three papers from elimination settings were included. These studies indicated two-dose VE estimates increased with increasing age at MCV1 and decreased as time since MCV increased.

A study from France analysed the relation between disease severity and vaccination status in over 10,000 measles cases reported between 2006 and 2019 and born since 1980. Compared to unvaccinated patients, the risk of severe measles was 71% to 83% lower in people vaccinated with two doses depending on the time since the last dose [10].

In Italy, the appropriate immunization strategy for internationally adopted children (IAC) is under debate and different approaches have been suggested. Boccalini et al. developed a decision analysis model to compare three strategies: presumptive immunization, pre-vaccination serotesting and vaccination based on documentation of previous immunization [11]. The strategy currently recommended in Italy (immunize based on documentation) is less expensive. From a cost-effectiveness point of view, vaccination based on serotesting results is the most advantageous strategy. Therefore, the serotesting strategy appears to be the preferred option in IAC.

Also in Italy, the cost-effectiveness of workplace vaccination against measles was assessed. In 2017, 22.3% of measles infections happened in hospital settings and 6.6% of cases occurred in healthcare workers (HCW)s. The immunization strategy with pre-vaccination screening was cost-saving compared to the vaccination without screening [12].

In a vaccination game, individuals respond to an epidemic by engaging in preventive behaviors that, in turn, influence the course of the epidemic. According to Flaig et al. such feedback loops need to be considered in the cost effectiveness evaluations of public health policies [13]. The example of mandatory measles vaccination and the role of its anticipation was elaborated using a SIR compartmental model with fully

rational forward looking participants who can therefore anticipate on the effects of the mandatory vaccination policy. Parents, eager and reluctant towards vaccination were included. The authors stated that individual anticipatory behavior may lead to a transient increase in measles prevalence before steady state eradication. This would cause non negligible welfare transfers between generations. Ironically, reluctant parents benefit the most from mandatory vaccination.

7.5.9 *Literature*

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*RIVM publication.

7.6 Meningococcal disease

M.J. Knol, W. Freudenburg-De Graaf, G. den Hartog, M. Ohm, W. Miellet, C. van Els, H.E. de Melker, N. van Sorge

7.6.3 *Key points*

- In 2019, the overall incidence of meningococcal disease decreased after an increase from 2015 to 2018.
- In April to June 2020, the number of cases was 80% lower than in the same period in the last five years, which may be (partly) related to the COVID-19 measures that were in place during these months, including social distancing and school closures,.
- The number of cases with meningococcal serogroup C disease is still very low, with six cases reported in 2019.
- The vaccination uptake of the MenACWY vaccination campaign in 2018/2019 among 14-18 year olds was 84% and an additional 2% of the eligible population got vaccinated prior to the campaign. A lower uptake was observed when parents were born abroad, especially for parents born in Morocco or Turkey.
- In 2019, the incidence of meningococcal serogroup W (MenW) disease decreased to 0.39 per 100,000 (n=62), after an increase in the number of cases from 2015 to 2018. In the first six months of 2020, only eight cases have been reported with no cases reported in April to June.
- The decrease of MenW in 2019 and the first months of 2020 was observed in vaccinated as well as unvaccinated age groups.
- Among children eligible for MenACWY vaccination at 14 months, there has been one vaccinated and one unvaccinated MenW case. Among adolescents eligible for MenACWY vaccination, there have been no MenW cases.
- 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 2019, 72 cases and five deaths of MenB disease were reported, which was similar to 2018 (74 cases and five deaths). The incidence of MenB disease was highest in children aged under 5 years, with 22 cases in 2018 (2.5 per 100,000).
- The number of cases of meningococcal disease caused by serogroup Y or other serogroups is low and stable.

7.6.4 *Figures*

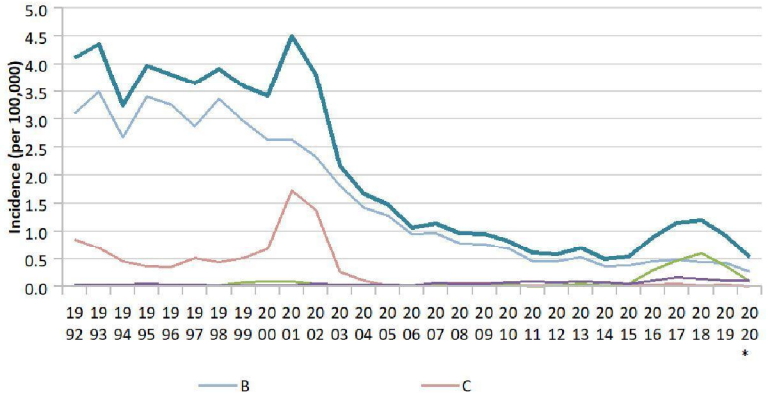

Figure 7.6.1 Incidence of meningococcal disease by serogroup, 1992-2020 (*up to June)*

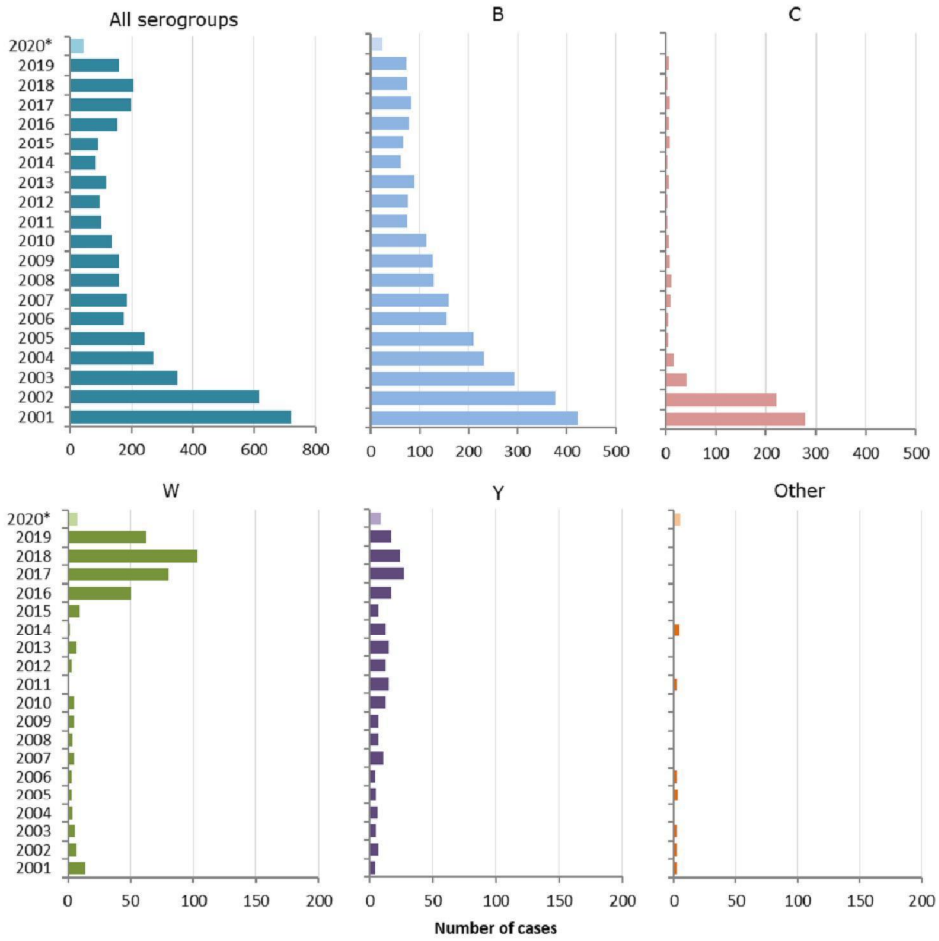

Figure 7.6.2 Number of cases of meningococcal disease by serogroup, 2002-2020 (*up to June)*

Note the different scale in the graphs

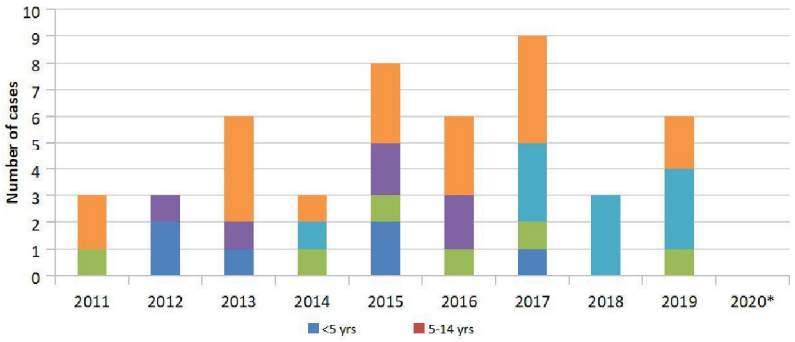

Figure 7.6.3 Number of cases of meningococcal serogroup C disease by age group, 2011-2020 (*up to June)*

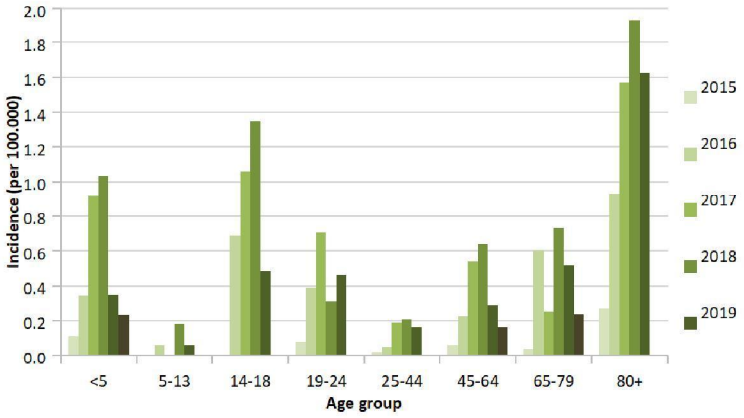

Figure 7.6.4 Age-specific incidence of meningococcal serogroup W disease by year, 2015-2020 (*up to June)*

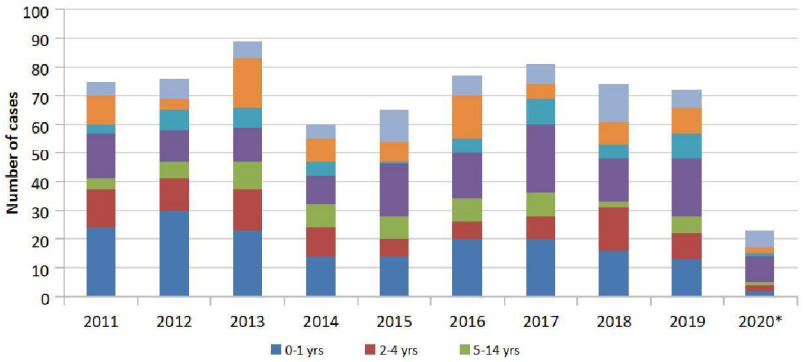

Figure 7.6.5 Number of cases of meningococcal serogroup B disease by age group, 2011-2020 (*up to June)*

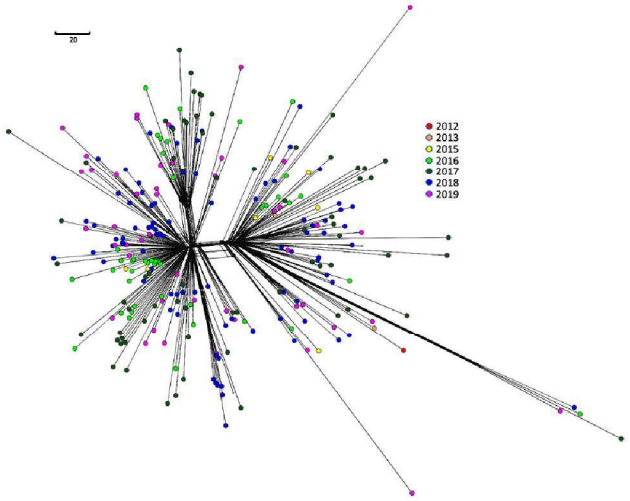

Figure 7.6.6 Neighbour-net phylogenetic network analysis of all available genomes of serogroup W clonal complex 11 isolates from the Netherlands, 2012–2019 (n =266)

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).

7.6.5 *Epidemiology*

7.6.5.1 Meningococcal disease

The incidence of meningococcal disease declined from 4.5 per 100,000 in 2001 to 0.49 per 100,000 in 2014 (Figure 7.6.1). From 2015 it increased to 1.2 per 100,000 in 2018 and in 2019 the incidence decreased to 0.92 per 100,000; these changes were mainly due to changes in serogroup W disease (see section 7.6.3.3). In the first six months of 2020 only 45 cases have been reported, which was much lower than in the same period in previous years (n=98 in 2019). Especially in April to June 2020 the number of reported cases was very low (80% lower than in the previous five years), which may be related to the COVID-19 measures that were in place during these months, including social distancing and school closures.

7.6.5.2 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 2019, six cases of MenC were reported, which is 4% of all meningococcal cases. One patient was between 15 and 24 years of age and was not vaccinated against MenC. The other cases were all 45 years or older (Figure 7.6.3). Up to June 2020, no MenC cases were reported.
Since the introduction of the conjugated MenC vaccine in 2002, there have been 16 MenC cases that were eligible for vaccination according to their date of birth (either for the 14-month program or the catch up campaign in 2002). Seven of these cases were unvaccinated, five were vaccinated and in four cases the vaccination status was unknown. The five vaccinated cases were between 16 and 26 years when diagnosed. Two of the patients had an underlying immune deficiency.
None of the MenC cases in 2019 died. Since 2015, one MenC case has died resulting in a case fatality rate of 3% (1/31).

7.6.5.3 Meningococcal serogroup W

Since May 2018, MenACWY vaccination at 14 months of age is part of the national immunisation programme. Between October 2018 and June 2019, all children born between January 1st 2001 and December 31st 2005 (14-18 year olds) were offered MenACWY vaccination. Vaccination uptake during the vaccination campaign was 84% and an additional 2% of the population got vaccinated prior to the campaign (3). From 2020 onwards, MenACWY vaccination is offered to children in the year they turn 14 as part of the national immunisation programme.
The incidence of MenW disease increased between 2015 and 2018, with a peak incidence of 0.60 per 100,000 in 2018 (n=103) (Figures 7.6.1 and 7.6.2). In 2019, the incidence decreased to 0.39 per 100,000 (n=62); 39% of all meningococcal cases were caused by serogroup W. In the first six months of 2020, only eight cases have been reported with no cases reported in April to June.
The increase in MenW disease between 2015 and 2018 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 2019, the incidence

decreased in vaccinated as well as unvaccinated age groups. The eight cases in the first three months of 2020 included one case under one year of age who was too young to be eligible for vaccination and seven cases of 45 years or older.
Among children eligible for MenACWY vaccination at 14 months, there have been two MenW cases (both were two years old), of which one was vaccinated and one was unvaccinated. Among adolescents who were eligible for MenACWY vaccination in 2018-2020, there have been no MenW cases. These data suggest good effectiveness of MenACWY vaccination in the vaccinated age groups. Whether the decrease in incidence in other age groups is due to implementation of MenACWY vaccination is uncertain as the decrease was already seen at the beginning of 2019 when the vaccination campaign was still ongoing.
Since 2015, 49 out of 305 (16%) MenW cases have died, with nine deaths reported in 2019. Deaths occurred in nearly all age groups, with the highest case fatality rate in 14- to 24-year-olds (16/61=26%). None of the eight MenW cases that were reported in the first six months of 2020 died.

7.6.5.4 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 2019, 45% of all meningococcal cases were serogroup B. In total, 72 cases of MenB disease were reported (Figure 7.6.2). Up to June 2020, 23 MenB cases were reported, which was much lower than in the same period in 2019 (n=41). Especially the number of reported cases in April to June was lower than in the previous years, which may be related to the COVID-19 measures.
In 2019, the incidence of MenB disease was highest in children aged under five (2.5 per 100,000, n=22), followed by 15- to 24-year-olds with an incidence of 0.9 per 100,000 (n=20) (Figure 7.6.5). In the first six months of 2020, especially the number of cases in children aged under five was very low with only four cases compared with on average 16 cases in the same period in the last five years.
Since 2015, 18 out of the 364 (5%) MenB cases have died. There were five deaths among MenB cases in 2019 (7%). Case fatality rates are comparable between age groups. In the last five years, 1-3 children under five years of age died of MenB disease each year.

7.6.5.5 Meningococcal serogroup Y

The incidence of meningococcal serogroup Y (MenY) disease has increased slightly over the last 3-4 years with an incidence of 0.10 per 100,000 in 2019 (n=17) (Figure 7.6.1 and 7.6.2). In 2019, 11% of all meningococcal cases were serogroup Y. In the first six months of 2020, nine MenY cases have been reported, which was rather similar to the number of cases in the same period in previous years. Most cases were adults aged 45 years or older (13/17 in 2019 and 7/9 in 2020). There have been no MenY cases in the children or adolescents who were eligible for MenACWY vaccination. Since 2015, 7 out of 87 (9%) MenY cases have died.

7.6.5.6 Other meningococcal serogroups

In 2019, one case of meningococcal disease due to a non-groupable meningococcus was reported (Figure 7.6.2). In the first six months of

2020, there were two cases of meningococcal disease due to serogroup X, one case due to serogroup E and two cases due to a non-groupable meningococcus. Meningococcal disease due to serogroups X and E is rare in the Netherlands with six and eight reported cases, respectively, between 2001 and 2019. These serogroups are also rare in other European countries. Also meningococcal disease due to a non-groupable meningococcus is rare with eight reported cases between 2001 and 2019 and occurs mainly in individuals with immune disorders, which was also true for one of the two cases in 2020.

7.6.6 *Pathogen*

Almost all serogroup W strains from 2015 to 2019 had the same finetype P1.5,2:F1–1 (263/292; 90%) and belonged to clonal complex 11 (cc11; 262/276; 95%). Figure 7.6.6 shows a cluster analysis of all available genome sequences of serogroup W cc11 meningococci isolated in 2012-2019 from Dutch patients. In 2016 and 2017, isolates from the same year seemed to cluster, but for isolates from 2018 and 2019 there was no clear clustering anymore.

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, 11 in 2019; up to June 2020 no MenB cases with this finetype were reported. 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 from 2016-2018 belonged to cc32 (20/22; 91%). In 2019, 6 of 9 isolates (67%) belonged to cc32. Of 33 B:P1.22,14:F5-1 cases since 2016, 12 lived in GGD region Rotterdam Rijnmond and an additional eight cases lived in other GGD regions in the south-west of the Netherlands. Most cases (17/33; 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. Overall coverage of MenB isolates from June 2017 to June 2019 was 73%.

From 2017 to 2019, 469 received meningococcal isolates were assessed by whole genome sequencing. As described above, the vast majority of serogroup W isolates belonged to cc11 (96%). Among serogroup Y, cc23 was the dominant clonal complex (75%). Serogroup B isolates consisted of 12 different clonal complexes, with 85% of assigned isolates belonging to cc32 (36%), cc41/44 (22%), cc269 (13%), or cc213 (14%). Among 15 serogroup C isolates, most belonged to cc11 (67%).

7.6.7 *Current/ongoing research at RIVM*

Conjugated polysaccharide vaccines protect against meningococcal disease but also reduce carriage of vaccine-type *Neisseria meningitidis* strains. In the fall of 2018, Miellet et al. investigated meningococcal carriage in young adults at the time of MenACWY vaccine introduction in The Netherlands and explored the feasibility of testing saliva. Paired saliva and oropharyngeal swabs were collected from 299 college students and tested for meningococci using conventional culture and molecular method of qPCR. Altogether 84 (28.1% of 299) students were identified as carriers of meningococcus by any method used. Carriage of serogroups B, Y, W, C, and A was 8.7%, 6.7%, 1.3%, 0.7%, and 0%,

respectively. All serogroup W strains (n=4) belonged to the hyperinvasive cc11 clone and distribution of other clonal complexes resembled the distribution seen in the Netherlands for invasive meningococcal disease. Detection of meningococcus by qPCR showed that a similar number of students was identified as carrier with oropharyngeal swabs and saliva. Saliva can, therefore, be considered in the surveillance of meningococcal carriage.

The uptake of the MenACWY vaccination campaign of 2018 and 2019 among adolescents born between 2001 and 2005 was 84% as calculated from the national vaccination register (4). Before the start of the campaign, already 1.9% of the eligible adolescents was vaccinated, which was estimated from the number of vaccines administered by Municipal Health Services and dispensed by public pharmacies. Possible determinants of vaccination uptake after the first invitation and recall were investigated among the first group invited for vaccination (born in May-December 2004) using random forest classification analysis. The most important predictor of vaccination after the first invitation was parents' country of birth (lower uptake when parents were born abroad, range: 52%-Morocco to 88%-Netherlands). The most important predictors after the recall were, respectively, distance to vaccination location (lower uptake with larger distance, range: 4-6%), percentage of votes for the conservative Christian (reformed) party in the municipality (lower uptake with higher percentage, range: 4-5%) and parents' country of birth (higher uptake when parents were born abroad, range: 4%-Netherlands to 11%-Syria). The recall strategy enhanced the uptake and was valuable to diminish immunization disparities. Future vaccination campaigns should put more effort into reaching adolescents with immigrant parents.

Persistence of vaccine-induced serological protection is necessary to protect individuals against invasive meningococcal disease, especially in epidemics like the recent Dutch MenW epidemic. However, meningococcal serogroup ACWY polysaccharide-specific antibodies wane after a single MenACWY-TT conjugate vaccination. Blood samples were collected before, 1 month, 1 year and 5 years after a single MenACWY vaccination from 50 healthy adolescents aged 15-20 who were once primed with a MenC conjugate vaccine at young age, and 130 adults (aged 55-70) who were naïve to meningococcal vaccination. Functional antibodies were measured 5 years after a single MenACWY vaccination in both cohorts to predict long-term persistence of serological protection. Protective rSBA titers (≥8) against MenC, MenW or MenY were present in 94-96% of the adolescents 5 years after vaccination. However, adults only showed protective rSBA titers in 32%, 65% and 71% against MenC, MenW and MenY, respectively. Only 25/130 (19%) adults were still protected after 5 years against all three serogroups tested. Functional meningococcal antibodies seem to decline quicker in adults than in adolescents, especially the functional antibodies for MenC. Protection at adolescent age after a MenACWY-TT vaccination when primed with MenC at young age was estimated to be long-lasting using a bi-exponential decay modelling. In contrast, when a meningococcal vaccination is administered to middle-aged adults, a single MenACWY-TT vaccination might not be sufficient for long-term persistence of seroprotection.

MenB vaccination is not included in the Dutch National Immunization Program but is indicated for special groups such as immunocompromised patients. 4CMenB is a multicomponent, protein-based vaccine against MenB consisting of factor H-binding protein, Neisserial heparin binding protein, Neisserial adhesion A and outer membrane vesicles containing Porin A. The RIVM has developed tools and reagents to test vaccine immunogenicity and vaccine-mediated humoral protection to *N. meningitidis* serogroup B. We could show that in children with various complement deficiencies 4CMenB vaccination elevated MenB specific antibodies, which could only kill bacteria through classical serum bactericidal activity with autologous complement if the complement defect was in the alternative pathway but not in the late terminal pathway (5). Irrespective of the complement defect, however, post-vaccination antibodies were shown to be effective by opsonophagocytosis, supporting the recommendation to vaccinate children with a complement deficiency against MenB.

7.6.8 *(Inter)national developments*

7.6.8.1 Carriage

Watle et al. studied meningococcal carriage and its risk factors among Norwegian adolescents and young adults in 2018-2019 (6). Among 2296 12–24-year-olds (majority 13–19-year-olds) meningococcal carriage was identified in 167 (7.3%) individuals. The highest carriage rate was found among 18-year-olds (16.4%). Among carriage isolates, 33.5% was genogroup Y, 9.0% genogroup B, 2.4% genogroup X, 1.8% genogroup C and 1.8% genogroup W. Clonal complexes cc23 (35.9%) and cc198 (32.3%) dominated and 38.9% of carriage strains were similar to invasive strains currently causing IMD in Norway. Use of Swedish snus (smokeless tobacco) (OR 1.56, 95% CI 1.07–2.27), kissing >two persons/month (OR 2.76, 95% CI 1.49–5.10) and partying >10 times/3months (OR 3.50, 95% CI 1.45–8.48) were associated with carriage, while age, cigarette smoking, sharing of drinking bottles and meningococcal vaccination were not.

7.6.8.2 Meningococcal disease

Campbell et al. assessed the relationship between meningococcal capsular group, age, clinical presentation, diagnosis and outcome among invasive meningococcal disease (IMD) cases diagnosed in England during 2014 (7). In 2014, there were 340 laboratory-confirmed IMD cases caused by MenB (n=179), MenW (n=95) and MenY (n=66). Clinical presentation with meningitis alone was more prevalent among MenB cases (28%) and among 15-24 year-olds (20%), whilst bacteraemic pneumonia was most prevalent among MenY cases (26%) and among ≥65 year-olds (24%). Gastrointestinal symptoms were recorded preceding or during presentation in 15% (40/269) of the cases with available information, including 5% (7/140) MenB, 17% (8/47) MenY and 30% (25/82) MenW cases. Upper respiratory tract symptoms were reported in 16% (22/141) MenB, 23% (11/47) MenY and 31% (26/84) MenW cases. Increasing age was also independently associated with bacteraemic meningococcal pneumonia, with no cases among 5-14 year-olds compared to 24% in ≥65 year-olds. Case fatality rates increased with age but no significant associations between serogroup and death were identified.

7.6.8.3 MenB disease

In September 2015, the UK introduced the 4CMenB vaccine into its national immunization program for infants with two primary doses at two and four months and a booster dose at 12 months. Ladhani et al. evaluated the effect of vaccination on the incidence of meningococcal group B disease during the first 3 years of the program (8). From September 2015 through August 2018, the incidence of meningococcal group B disease in England was significantly lower in vaccine-eligible cohorts than the expected incidence (63 observed cases as compared with 253 expected cases) with a 75% reduction in age groups that were fully eligible for vaccination (incidence rate ratio: 0.25; 95% CI: 0.19-0.36). The adjusted vaccine effectiveness against meningococcal group B disease (estimated with the screening method) was 52.7% (95% CI: −33.5 to 83.2) after two primary doses and 59.1% (95% CI: −31.1 to 87.2) after two primary doses and a booster dose. Over the 3-year period, there were 169 cases of meningococcal group B disease in the vaccine-eligible cohorts, and an estimated 277 cases (95% CI, 236 to 323) were prevented.

Marshall et al. performed a cluster randomized trial to assess the effect of the 4CMenB vaccine on meningococcal carriage in 15-18 year olds in Australia (9). Among 237 participating schools, 24,269 students were enrolled in the study during April through June 2017. One year after vaccination, there was no difference in the prevalence of carriage of disease-causing *N. meningitidis* between the vaccination group (2.55%; 326 of 12,746) and the control group (2.52%; 291 of 11,523) (adjusted odds ratio: 1.02; 95% CI: 0.80-1.31). Among carriers, also the carriage density did not differ between vaccinated and unvaccinated students (mean difference: 0.04; 95% CI: -0.19 to 0.27) (10). This study showed no effect of 4CMenB vaccination on carriage and carriage density, and therefore this vaccine is not expected to prevent transmission or provide herd protection.

7.6.8.4 MenW disease

Barret et al. describe a cluster of three MenW cases, including two deaths, at a university campus in 2016 in France (11). The three cases occurred within a 2-month period among students in different academic courses. All three isolates were identical and belonged to the "UK-2013 strain" phylogenetic branch. The attack rate was 10.8/100,000 students. A vaccination campaign was organized 15 days after the third case occurred. In total, 13,198 persons (41% of students and 35% of staff) were vaccinated. No further cases occurred at the campus in the year following the vaccination campaign.

Villena et al. describe the MenW incidence in Chile from 2009-2016 and assess the impact of a MenACWY vaccination campaign implemented in 2012 targeting children of nine months to four years (12). The MenW incidence rose from 0.01/100,000 inhabitants in 2009 to a maximum of 0.6/100,000 in 2014. Infants and adults 80 years of age and older were mostly affected. In the group of children from 1 to 4 years of age MenW incidence declined from 1.3/100,000 in 2012 to 0.1/100,000 in 2016, a 92.3% reduction after vaccination implementation. In the same period and age cohort, the case fatality rate decreased from 23% to 0%. No indirect effects of vaccination were observed.

7.6.8.5 Cost-effectiveness

Serogroup B meningococci are the largest cause of invasive meningococcal disease in Canada. Breton et al. assessed the cost-effectiveness of three adolescent MenB-FHbp immunization strategies (13). These strategies included routine vaccination with MenB-FHbp at: (1) 14 years, along with existing school-based programs, with 75% uptake; (2) 17 years with 75% uptake, assuming school vaccination; and (3) 17 years with 30% uptake, assuming vaccination outside of school. With no vaccination, an estimated 3974 MenB cases would be expected over 30 years. Vaccination with strategies 1–3 were estimated to avert 688, 1033, and 575 cases, respectively. These outcomes were associated with incremental costs per quality-adjusted life-year of $976,000, $685,000, and $490,000 respectively. Therefore, MenB vaccination is unlikely to meet widely accepted cost-effectiveness thresholds.

In Australia, MenACWY vaccination is included in the NIP and is indicated for infants aged 12 months. Si et al. assessed the cost-effectiveness of a broader MenACWY vaccination program for Australians aged 15 to 19 years (14). The total cost for MenACWY vaccination was AU$56 per dose. Costs and health outcomes were discounted by 5% per annum in the base-case analysis. Compared to no vaccination, a MenACWY vaccination program targeted at Australians aged 15–19 years was expected to prevent 1664 invasive meningococcal disease cases in the Australian population aged 0–84 years. The program would lead to 2058 quality adjusted life years (QALYs) gained at a total cost of AU$115 million. This equated to an incremental cost-effectiveness ratio of AU$55,857 per QALY gained. Therefore, the MenACWY immunisation program targeted to Australians aged 15 to 19 years is likely to be cost-effective.

7.6.9 *Literature*

7.6.9.1 References

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*RIVM publication

7.6.9.2 Other RIVM publications

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7.7 Mumps

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7.7.3 *Key points*

- The incidence of mumps in 2019 was low (0.8 per 100,000), but double that of the previous year.
- From January to March 2020, mumps notifications were double that of 2019 for the same period, however, a sharp decrease was seen from 1 April 2020 which coincided with control measures that were put in place in response to the COVID-19 pandemic.
- Most of the mumps cases in the Netherlands were caused by mumps virus genotype G.

7.7.4 *Tables and figures*

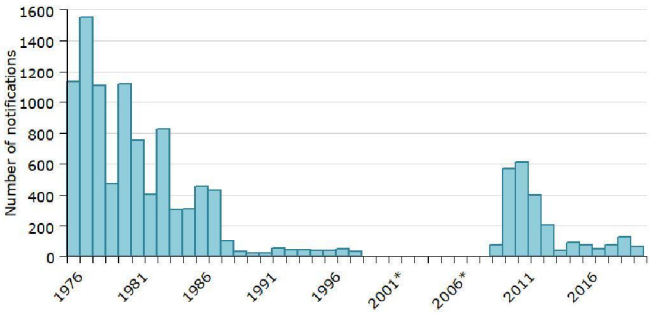

Figure 7.7.1 Number of notified mumps cases in the period 1976-2020
* In the period 1999-2008 mumps was not notifiable
Year 2020: up to 1 May
Source: Osiris

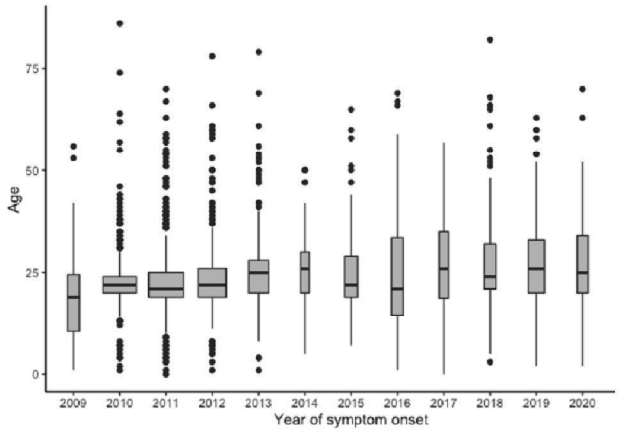

Figure 7.7.2 Age distribution of mumps cases by year in the period 2009-2020.
Year 2020: up to 1 May
The horizontal line which divides the box into two parts indicates the median age, the middle box includes 50% of the values, and the vertical line outside of the box shows the lowest and highest age. Age values which fall outside of the box and vertical line are outliers and are represented by dots.
Source: Osiris

7.7.5 *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 1500 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 the epidemic period (2010-2012), the mean age of reported mumps cases was 23.1 which increased to 26.7 in the years (2013-May 2020) ($p<0.001$) (Figure 7.7.2).

In 2019, 131 cases of mumps were reported (Figure 7.7.1). Among them, males (n=85) were almost double compared to females (n=46) with a mean age of 27 years (range 2-63). Forty-four students were reported with mumps. Ninety-seven cases (79%) were vaccinated; 19 (20%) with one dose, 68 (70%) with two doses, 5 (5%) with three or more doses of vaccine, and 5 (5%) were vaccinated with an unknown number of doses. The vaccination status was not known for the eight remaining cases. On average, the 26 unvaccinated cases were 36 years old (range 4-60). Six patients were hospitalised aged between 19 and 34 years; two of these reported orchitis and one pancreatitis. In addition, nine adults reported complications; eight reported orchitis and one reported orchitis or encephalitis. Among men, orchitis was less prevalent in vaccinated men (5%) compared to unvaccinated men (38%) ($P<0.001$).

Seventeen percent of the cases (n=22) acquired the infection abroad and country of infection is unknown for four persons. Twelve clusters including 50 patients in total were identified in 2019. The largest cluster occurred among attendees of a party and/or secondary school where 12 persons aged between 22 and 46 years were reported with mumps. The second largest cluster involved nine persons who were students or had contact with students and were aged between 20 and 26 years. The remaining 10 clusters consisted of between two and four persons occurring in close-contact settings between either friends, partners, family, or work colleagues.

In 2020, until 1 May, 61 mumps cases have been reported which is higher than for the same period in 2019 (42 cases). In early March 2020, control measures were put in place nationwide in response to the COVID-19 pandemic and from 1 April 2020, a decrease in the number of mumps notifications was seen. As the average incubation period for mumps is between 16 and 18 days, this shows that the decrease coincided with control measures that were put in place. There were more male (57%) patients than female and the mean age was 27 years (range 2-70). Seventeen students were reported and six acquired the infection abroad. In addition, nine persons acquired the infection abroad and country of infection is unknown for four persons. Most cases (n=38, 62%) did not have an epidemiological link, except for eight clusters identified in 2020. All eight clusters included between two to four persons. Three of the eight clusters, included one or more persons who travelled abroad and are most likely imported cases.

7.7.6 *Pathogen*

In the past decade, most mumps cases in the Netherlands were caused by infection with genotype G mumps viruses. In 2019 and the first five months of 2020, a genotype was obtained from mumps viruses detected in 117 cases. The majority of these cases (94%) was genotype G. In addition, 3 other genotypes were detected in a small amount of cases: genotype K (2 cases), H (2 cases) and C (3 cases). Three of the cases with non-G genotypes were imported cases from non-European countries.

7.7.7 *Research*

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

7.7.7.1 Molecular surveillance

In addition to sequencing of the SH protein gene and adjacent non-coding regions (SH; 316 nucleotides) to determine the mumps virus genotype, genome information can be used to analyse the molecular epidemiology. Additional genome information can be obtained to study the increase the molecular resolution. Currently published protocols focus on sequencing of three non-coding regions (NCRs), or the HN and F protein genes or the complete genome [2-5]. Analysis of sequence data from the SH and NCRs of mumps genotype G viruses detected in the Netherlands between 2017 and 2019 revealed that two major genetic lineages were present in these years. Results were confirmed by

analysis of 8 complete genomes from recent mumps genotype G viruses detected in the Netherlands. This indicates that mumps genotype G viruses continued to circulate in the Netherlands and surrounding countries in these years. Furthermore, comparison of molecular resolution obtained with SH and NCRs with complete genomes obtained with next-generation sequencing clearly indicated that additional molecular resolution can be obtained by analysing complete genomes [6]. This can be helpful to support epidemiological data or show transmission links that can not be identified by epidemiological data. From 1 October 2019 to 31 March 2020, 14 epidemiological clusters (including 46 cases) were identified where two or more cases met the mumps notification criteria and had an epidemiological link to a confirmed case with a date of symptom onset between this period. Eleven of the 14 clusters (including 24 cases) were confirmed as clusters using molecular sequencing as the mumps viruses were detected with identical SH+NCRs sequences (manuscript currently in preparation).

7.7.7.2 Humoral and Cellular immunity

The re-emergence of mumps among vaccinated young adults has become a global issue. Mumps-specific antibody titers are the current standard to assess immunity against the mumps virus. Globally waning of the vaccine-induced antibody titers is observed. In addition, suboptimal induction of T-cell responses may also reduce protection. To investigate the mechanisms involved, over the past years longitudinal blood samples from a small cohort of clinically symptomatic mumps cases (n=27) were collected for immunological interrogation in the Immfact natural infection study. To evaluate waning of mumps-specific IgG antibodies longitudinal serum samples were tested in a multiplex immunoassay (MIA). Preliminary results are expected end of 2020. In 2018, we observed a dominant polyfunctional CD8+ T-cell response after natural mumps virus infection that was not present after vaccination [7]. Now, we have identified the first 41 naturally processed CD8+ T-cell epitopes of mumps virus that are conserved amongst various mumps virus strains [8]. HLA-A0201+ restricted CD8+ T-cell responses to 6 epitopes were confirmed in blood samples of mumps cases. The identification of CD8+ T-cell epitopes of mumps virus makes it possible to monitor the CD8+ T cell response after mumps infection and vaccination. This may lead towards a better understanding of mumps vaccine failure, and it could provide clues for interventions to prevent this, such as an extra MMR vaccination [9-12].

7.7.7.3 Clinical MMR-3 study

In 2019, we reported that MMR-3 vaccination is expected to be an effective and safe intervention for controlling a mumps outbreak among young adults based on an immunogenicity and safety study that we performed [9]. In May 2020, collection of extra follow-up samples for this study were completed to be able to determine mumps-specific antibody levels up to 3 years post-MMR-3 vaccination.

7.7.8 *International developments*

In Europe, other countries have reported an increase in the number of mumps cases in 2019 compared to previous years. In England, the number of laboratory confirmed mumps cases in 2019 was the highest number of cases reported since 2009 [13]. This large increase has been

driven by outbreaks in universities and colleges. Ireland also reported a notable increase in mumps cases in 2019 compared to previous years with the highest number of notifications observed in the age group 15-24 years [14]. In both England and Ireland, it was noted that many of the mumps cases in 2019 were from the same birth cohort most affected by low MMR1 vaccination uptakes in the late 1990s and early 2000s [13, 14].

In the United States, research has been carried out to assess waning immunity as a key contributing factor to mumps resurgence. Among participants, it was found that the frequency of circulating mumps specific memory B cells was 5 to 10 times lower than measles and rubella, and 10% of the participants had no detectable memory B cells to mumps. Additional strategies are needed to improve the quality and durability of vaccine-induced immunity [15].

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* RIVM publication

7.8 Pertussis

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7.8.3 *Key points*

- In 2019, the overall incidence rate (IR) of pertussis notifications was 36.8 per 100,000 compared with 28.4 per 100,000 in 2018.
- In 2020 up to April 1st, the IR was 16.6 per 100,000; this IR was probably affected by the control measures in view of the covid-19 pandemic.
- In April and May 2020, vaccination coverage of the maternal pertussis vaccination was estimated to be about 70%.
- In 2019, estimates for the effectiveness of the maternal pertussis vaccination in preventing pertussis in 0-3-month-olds was 73%-90%s , assuming a 20%-40% vaccination coverage. For 2020, the VE amounted to 93%-97%, taking into account 50%-70% coverage.
- The prevalence of prn-deficient strains in the Netherlands sharply increased in 2018-2020.

7.8.4 *Tables and figures*

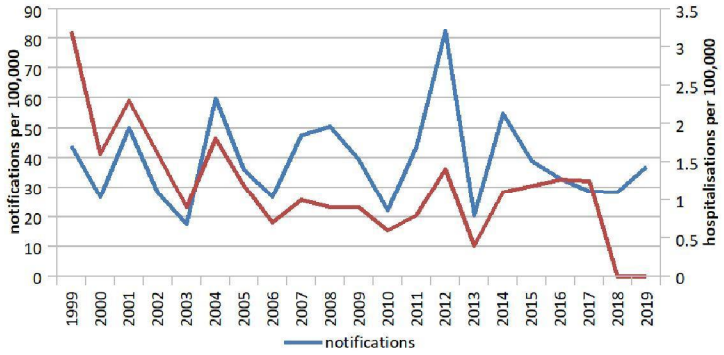

Figure 7.8.1 Pertussis notifications (left Y-axis) and hospitalizations (right Y-axis) per 100,000 for 1999-2019 Source: OSIRIS, Statistics Netherlands
No hospitalization data from 2018 onwards is available yet.

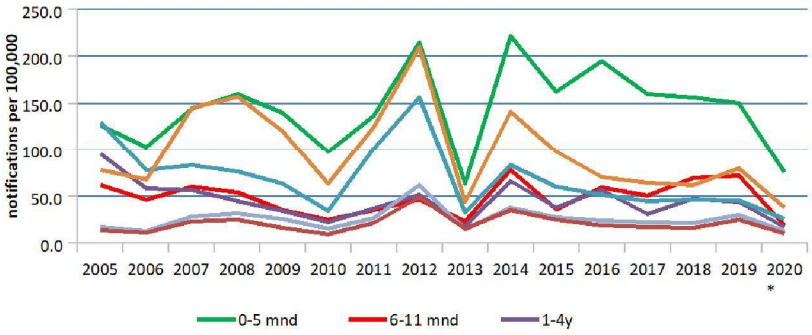

*Figure 7.8.2 Pertussis notification per 100,000 per age category for 2005-2020**
Source: OSIRIS
*reports up to April 1st 2020 are included

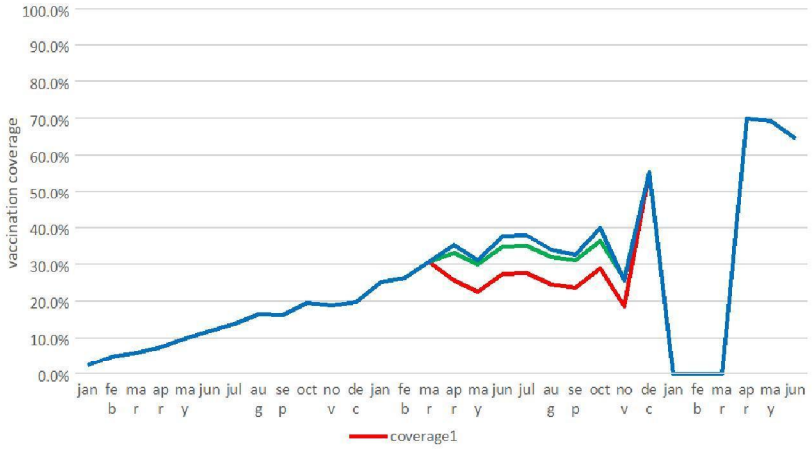

Figure 7.8.3 Estimated vaccine coverage of the maternal pertussis vaccine, from 2018 - 2020, July 1st. Up to April 2019, all coverage estimates are the same. From April to November 2019, coverage1 represents the coverage without data from the Municipal Health Services (MHS). Likewise, coverage2 represents the coverage with a fixed number of vaccinations (n=1000), administered via MHS and coverage3 reflects the coverage in which the number of MHS-vaccinations is 0.37 of the number of SFK vaccinations.
Source: Statistics Netherlands, SFK data, municipal health services, Praeventis.

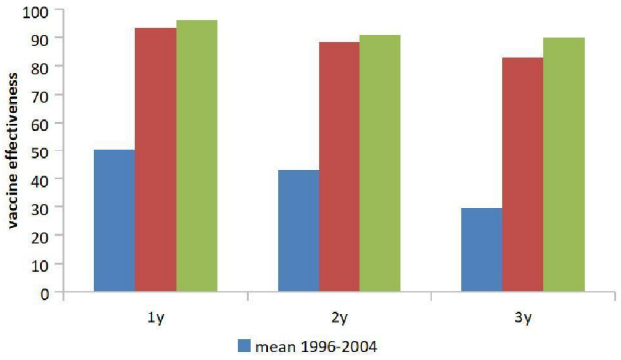

Figure 7.8.4 Vaccine effectiveness of the primary pertussis vaccination, calculated with the screening method, estimated for 1,2, and 3-year-olds during the use of whole-cell pertussis vaccination (mean 1996-2004 and during the use of the acellular pertussis vaccination (mean 2005-2018, and 2019 separate) Source: OSIRIS, National vaccination coverage report*

*For 2017 a population coverage of 94% was used and for 2018 and 2019 a coverage of 93%. For all other years, a population coverage of 96% was used.

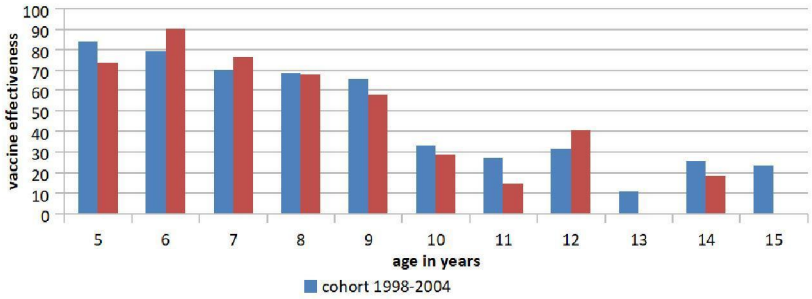

Figure 7.8.5 Mean vaccine effectiveness of the pre-school booster, calculated with the screening method, estimated for 5 to 15-year-olds for the whole cell pertussis priming cohorts (1998-2004) and the acellular pertussis priming cohorts (2005 and younger). Not all cohorts of 2005 and younger have yet reached the age of 10-15 years. Source: OSIRIS , National vaccination coverage report*

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

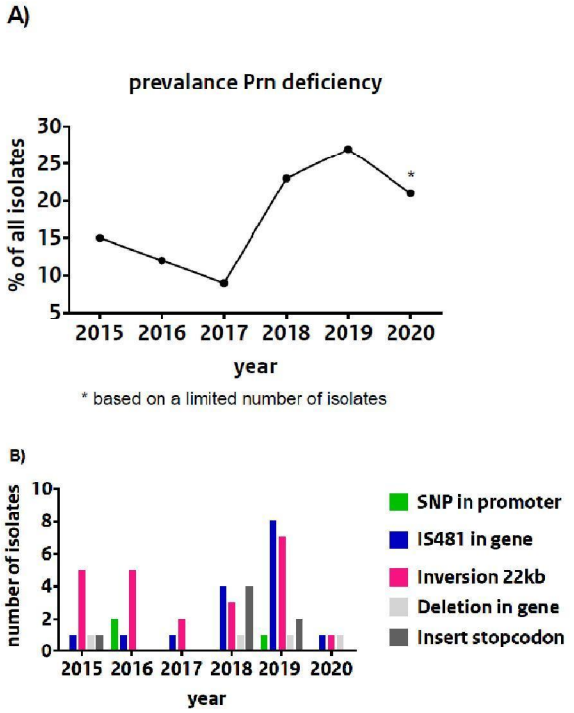

Figure 7.8.6 Prevalence (A) and molecular mechanism (B) of loss of pertactin (Prn) production in clinical isolates collected between 2015 and 2020.*
*: isolates till May 1, 2020 are included

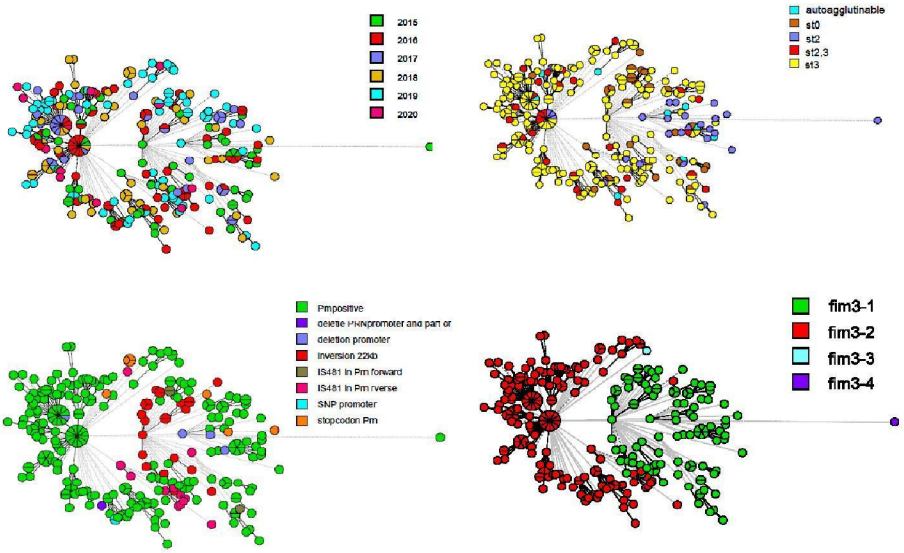

Figure 1.8.7 Genetic relationship between 271 clinical isolates based on wgMLST, with clustering based on year (A) and serotype (B), the genetic relationships between Prn-strains by molecular mechanism (C) and Fim3 subtype (D)

7.8.5 *Epidemiology*

7.8.5.1 Disease

In 2019, the overall incidence rate (IR) of pertussis notifications was higher than in 2018 (36.8 per 100,000 vs 28.4 per 100,000). In 2020 up to April 1st, the IR was considerably lower, i.e. 16.6; maybe the IR was affected by the measures to prepare and control the outbreak of coronavirus. (Figure 7.8.1) The last epidemic peak in pertussis notifications was seen in 2014/2015, so the epidemiological rise in pertussis notifications in 2019 is conform expectations, with a peak pattern of 3-5 years in countries with a high vaccination coverage. Hospitalization data of 2018-2019 are not yet available.
The increase of IRs of notifications in 2019 is mainly due to rises in IRs in adolescents, adults and elderly. (Figure 7.8.2) IRs in the younger age groups remained stable. Looking at the first trimester of 2020 (January 1 – April 1), we see an decreased IR for all age categories. (Figure 7.8.2) For 0-5-month-olds, the decrease can also be due to the implementation of a maternal pertussis vaccination programme from December 16, 2019 onwards.
Five pertussis related deaths were notified in 2019. It concerned three elderly (70, 86 and 89 years old), of whom two had underlying cardio-respiratory conditions. Furthermore two 0-year-olds died. One was too young to be vaccinated and one received the first vaccination 2 weeks before the estimated disease onset. Statistics Netherlands reported 2 pertussis related deaths.

7.8.5.2 Maternal pertussis vaccination coverage

Since 2016, pregnant women were able to get a maternal pertussis vaccination at own cost. A maternal pertussis vaccination was introduced in the NIP from 16 December 2019 onwards. From that moment onwards, all pregnant women with a gestational age of 22+0w and can be vaccinated through the youth health care.
In 2016 and 2017, vaccination coverage of the maternal pertussis vaccination was <2% [1]. In 2018, vaccination coverage slowly increased to 20% (Figure 7.8.3). In 2019, it ranged between 19%-31%. In this estimate the maternal pertussis vaccinations, administered through the Municipal Health Services were not taken into account because they were not available. After correction for this bias, coverage increased to 40%.
During the first months of 2020, sort of catch up campaign occurred, during which pregnant women that were eligible for a maternal pertussis vaccination already before introduction in the NIP could be vaccinated. They might have postponed the vaccination because within the NIP de vaccination is free of charge. In April and May 2020 the catch up effect was not present anymore and the vaccination coverage was 63% and 59%, respectively.
For 2018-2020, the monthly number of pregnant women in 2018, retrieved from Perined, was used as numerator for all estimates; no more recent estimate was available.
For a description of the methodology, see appendix 1.

7.8.5.3 Vaccine effectiveness (VE)

In 2019, the estimate of effectiveness for the maternal dTap vaccination in preventing pertussis in 0-3-month-olds was 73% when assuming a 20% vaccination coverage. With 30% and 40% coverage, VE estimates increased to 84% and 90%, respectively. In 2020, VE estimate was 93%, taken into account 50% vaccination coverage. At 60% and 70% coverage, this VE increased to 95% and 97%, respectively. These estimates are in line with estimates from other countries [2].
Figure 1.8.3 shows the VE estimates of the infant series. Since the switch from whole-cell pertussis vaccine to an infant combination vaccine with an acellular pertussis component in 2005, the VE estimate 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 estimate shows a decrease after ~5 years, i.e. when children reach the age of 10 years (figure 7.8.4). This is in agreement with the notification rates of these age-groups, as the 10-19-year-olds have a higher IR compared to the 1-9-year-olds.
The VE's estimates described above, are calculated with the 'screening method'. The presented VE should not be interpreted as the 'true' absolute estimate of the effectiveness. It is merely a way to study the trend in VE estimations. See appendix 1 on surveillance methodology for details of the methodology to calculate VE.

7.8.6 *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. The strain surveillance focuses on the

changes in the genotype and phenotype of the *B. pertussis* family in the Netherlands. Confirmed *B. pertussis* strains are being 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 2019, a Bordetella species could be culture-confirmed from 65 out of 313 (21%) submitted samples, of which 63 were *B. pertussis*. Other species identified were *B. holmesii* (n=1) and *B. parapertussis* (n=1). Compared to 2017, RIVM largely extended its network of participating laboratories resulting in an increase of received samples. In 2019, Bordetella suspected specimens were obtained from 17 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, for a complete geographical coverage of The Netherlands. After week 16 of 2020, COVID-19 related restrictions in society resulted in a sudden and dramatic drop of pertussis notifications reported after diagnostic confirmation. Therefore, we also received only a minor fraction of the expected *B.pertussis* isolates in our surveillance program. We are committed to increase the number of isolates in the 2nd half of 2020, to have a clear picture of the current circulating strains in the Netherlands.
In The Netherlands, the national immunization program uses an acellular pertussis vaccine consisting of three pertussis antigens namely Ptx, FHA and Prn. The reemergence of pertussis has been attributed to several factors including bacterial strain adaptation due to vaccine pressure [3]. Therefore, carefully monitoring of the expression of vaccine targets, in particular Prn, by the bacteria is essential. A high frequency of Prn or FHA deficient *B. pertussis* isolates could be prognostic for vaccine evasion, leading to more pertussis cases.
Between 2010-2015, an emergence of *B. pertussis* isolates was seen that are deficient in the vaccine component Prn, with a prevalence of 10-15% in 2015 to 2017. However, in 2018 a sharp increase was seen, with Prn deficiency in 24% (11/46) of the clinical isolates. This alarming rise continued in 2019, with Prn deficiency in 27% of all isolates (19/71). In 2020 up to May 1st,, 21% (3/14) of the collected were found Prn-deficient (Figure 7.8.6A). Sequence analysis showed that an inversion of ~22 Kb in the promotor region was the most frequently found (n = 23) cause of prn-deficiency followed by an insertion of the IS481 element in the *prn*-gene (n = 17), and insertion of a stop-codon (n=6) as shown in figure 7.8.6B.
In 2018, one clinical strain was isolated that lacks the production of the acellular vaccine immunogen FHA. Results for FHA production for the strains collected in 2019 and 2020 are expected at the end of this year.

A 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 1.8.7 shows the genetic relationship between all 271 *B. pertussis* strains isolated between 2015 and 2018. No clustering of isolates based on year (Fig 7.8.7A) or serotype (Fig 7.8.7B) was observed, but distinct Fim3 subtype clusters could be identified (Fig

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.

7.8.7 *Research*

7.8.7.1 Cost effectiveness

In the United States, persons ≥11 years are recommended to receive one dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine, followed by decennial tetanus- and diphtheria-toxoid (Td) boosters. Many providers use Tdap instead of Td. Havers et al. evaluated epidemiologic and economic impacts of replacing Td boosters with Tdap [4]. At lowest incidence estimates, administering Tdap resulted in high costs per QALY saved ($8,972,848). As incidence increased, cost per QALY saved decreased rapidly. With incidence estimates of 250 cases/100,000 person-years and 500 cases/100,000, cost per QALY saved were $81,678 and $35,474 respectively. The authors conclude that replacing Td with Tdap for the decennial booster would not be cost-effective based on reported cases. If pertussis incidence, which is incompletely measured, is assumed to be higher than reported through national surveillance, substituting Tdap for Td may lead to moderate decreases in pertussis cases and cost per QALY.
In another American study, the cost-effectiveness of Tdap vaccination for Tdap-eligible adults aged 19 through 85 in the United States was evaluated [5]. The incremental cost-effectiveness ratios (ICERs) for vaccinating US adults aged 19 to 85 with Tdap ranged from $248,000/QALY to $900,000/QALY. Sensitivity analysis showed the most dramatic changes in ICER occurred when changing the underreporting factor, vaccine effectiveness and vaccination costs. Further investigation of the true burden of pertussis disease among adults and the effectiveness of Tdap vaccination in this population is needed to better estimate the impact of Tdap vaccination.
In Canada, pertussis immunization is administrated at 2, 4, 6, and 18 months, followed by a childhood dose at 4 to 6 years. Immunization of pregnant women between 27 and 32 weeks of gestation is recommended, with the goal of protecting infants. Additionally, in Ontario, pertussis immunization of adolescents at 14 years of age was introduced in 2003. Aniywe et al. assessed the cost-effectiveness of adolescent pertussis immunization strategies in Canada [6].
Three Tdap vaccination strategies were evaluated (1) immunization of 10 year olds, (2) removal of adolescent vaccination, and (3) immunization of 14 year olds (that is the status quo). The findings suggest that alternate adolescent Tdap vaccine strategies – either immunization of 10 year olds, or removal of the adolescent vaccine – are more cost-effective than the current practice of immunizing 14 year olds.
Sandmann et al. evaluated the cost-effectiveness of the maternal pertussis vaccination program in England, implemented in 2012 [7] Following the program, pertussis-related infant hospitalizations and deaths in 2012–2017 were assessed and compared with non-vaccination scenarios. Overall, the incremental costs per QALY gained from the program versus the non-vaccination scenarios ranged between £11 000–£28 200/QALY. Despite considerable uncertainties, findings support the cost-effectiveness of the program.

7.8.7.2 Immunology

7.8.7.1.1 Maternal pertussis vaccination

In the MIKI study, a group of pregnant women received dTap at 30-32w GA and was compared with a control group of unvaccinated pregnant women [8]. Memory B and T-cell responses have been determined pre and post booster vaccination at 11 months of age. Numbers of antigen - specific B-cell and T-cells were detectable one month post booster and were not affected by the maternal vaccination (Barug et al., manuscript in preparation).

7.8.7.1.2 Humoral immunity

In the cross-sectional, nationwide serosurveillance study more than 7000 serum samples have been collected during 2016 -2017. The specific IgG antibody levels against 3 vaccine antigens (PT, FHA and Prn) have been determined with the MIA and the analyses are ongoing at the moment. Preliminary data reveal that the proportion of recently infected individuals aged 10 years and above remained at the same level or a bit higher as in the serosurveillance study from ten years earlier (2006-2007). This implicates that the overall circulation of B. pertussis is on the same level. The vaccination coverage and thus participation to the NIP seems to increase in the orthodox reformed groups within the low vaccinations communities. In the natural infection Immfact study between 2015 and 2020 serum and saliva samples were collected longitudinally up to 3 years after symptomatic pertussis from 105 cases and at one time point from 156 age-matched healthy controls. IgG and IgA antibody levels against 9 antigens from *B. pertussis* were determined with an experimentally extended MIA. The first set of data indicating the pace of natural waning immunity and diversity of the antibody responses is expected end of 2020.

7.8.7.1.3 Innate and Cellular immunity to *B. pertussis*

Despite vaccination, pertussis remains capable of circulating and infecting individuals of all ages. This is due to a combination of waning or suboptimal immunity and emergence of *B. pertussis* strains that can escape or modulate pre-existing immunity. Evidence is accumulating that the initial priming of the specific cellular immunity to *B. pertussis*, steered by innate cells, determines the duration of the acquired protective immunity. The underlying mechanisms why natural infection or the previous whole cell pertussis vaccine induce a far more effective and durable immune response than the current acellular vaccine are being studied in detail in a PhD project. Priming of IFNγ and IL-17-type cellular immunity and avoidance of IL-4/IL-13 type cellular immunity seems to be crucial in durable protection to pertussis, and therefore an important hallmark for future improved pertussis vaccines, as recently reviewed [9]. Insight was gained in how *B. pertussis* can interact with local innate immune cells and epithelium cells to modulate subsequent cellular immunity [10]. In order to provide further understanding on the host defense mechanism against *B. pertussis,* the activation of macrophages and the cross-talk with other innate cells were investigated [11]. Together these findings highlight the importance of studying emerging *B. pertussis* strains and their modulatory effect on the immune response.

7.8.8 *International developments*

Within the framework of the EUPertstrain group, a collaboration between European experts on whooping cough, a seroprevalence study in European countries for pertussis, diphtheria and tetanus in the age groups 40-60 years has been conducted by the RIVM and funded by ECDC [12]. 18 Countries have participated and collected the requested sera (around 500). Measurement of the antibody levels against pertussis toxin (PT), diphtheria toxoid (DT) and tetanus toxin (TT) with the MIA has been completed resulting in a final database of around 30,000 values. The percentages of sera per country with a level for IgG-PT ≥100 IU/mL, indicative for a recent pertussis infection, varied between 1.8% (Finland)
and 9.4% (Norway) with 13/18 countries showing a level between 4.0% and 6.4 %. In the samples of the Netherlands, based on the Pienter3 serosurvey, 5.4% had IgG-PT ≥100 IU/ml. In addition, the GMC's of IgG-PT antibodies in all countries varied between 7-15 IU/mL, suggesting that the epidemiological situation for pertussis across EU/EEA is broadly similar. This cross-sectional retrospective seroprevalence study among middle-aged adults in 18 European countries showed that the circulation of B. pertussis is widespread despite highly implemented childhood vaccination programs (manuscript submitted).

The Periscope consortium, consisting of pertussis experts from 2 vaccine companies, 4 national institutes including the RIVM, and 16 European universities, are working on an extensive IMI-2 project. The main objective of this project is to unravel the difference in protective properties between the acellular pertussis vaccines, the whole cell pertussis vaccines and natural infection, and to characterize new biomarkers for protective immunity to *B. pertussis*. The role of the RIVM is to develop and apply immunological assays for the measurement of antibodies, T-cells and B-cells, and to conduct natural infection and clinical vaccine studies. An assay for the measurement of specific memory and plasma B cells was standardized and applied to show that colonization is an immunizing event in a novel human experimental infection model based on the well characterized RIVM-originating *B. pertussis* isolate BP1917 [13]. Also a highly standardized platform technique was developed within the consortium suitable to monitor CD4 T-cell dynamics in whole blood after vaccination or infections [14].
The multi-center BERT study, involving a booster vaccination in four different age groups, has started in October 2017, and has been completed including the longitudinal samples of 1 year after the booster by January 2020 in the Netherlands, the UK and Finland. Vaccine antigen-specific IgG and IgA antibody levels in the BERT samples before, 28 days after and 1 year after vaccination have been measured by the RIVM. Next to this, B-cell responses have been determined by measuring numbers of circulating antigen-specific plasma cells producing IgG and IgA around day 7 post booster. In addition antigen specific memory B-cell responses were determined pre-booster and at 28 days and 1 year post booster vaccination. Furthermore, novel *B. pertussis* specific T-cell tests are being developed, and a whole blood assay is being evaluated in the BERT study, as recently published [15].

7.8.9 *Literature*

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*RIVM publication.

7.9 Pneumococcal disease

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7.9.3 *Key points*

- In April and May 2020, the number of IPD dropped by 80% compared with the 5-year average, most likely related to COVID-19 measures. This influenced the overall and age-specific incidence and time trends of IPD in 2019/2020.
- In epidemiological year 2019/2020 (June to May), 43 children <5 years of age with IPD were reported, of which only one case was caused by a serotype included in the 10-valent PCV.
- In children <5 years of age, introduction of pneumococcal conjugate vaccination (PCV) in 2006 led to a large reduction of IPD. 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 covered by 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 89% (95%CI 72-96%) against vaccine type IPD.
- In 2020, PPV23 vaccination was to be offered to all 60-, 65-, 70- and 75-year-olds in the Netherlands. However, due to the COVID-19 pandemic, priority has been given to the oldest age groups, meaning that in Autumn 2020 all 73-79 year olds will be offered PPV23 vaccination.

7.9.4 *Tables and figures*

Figure 7.9.1 Number of cases of invasive pneumococcal disease (IPD) from June 2019 to May 2020 reported by nine sentinel labs (covering ~25% of the Dutch population) by month compared with the 5-year moving average

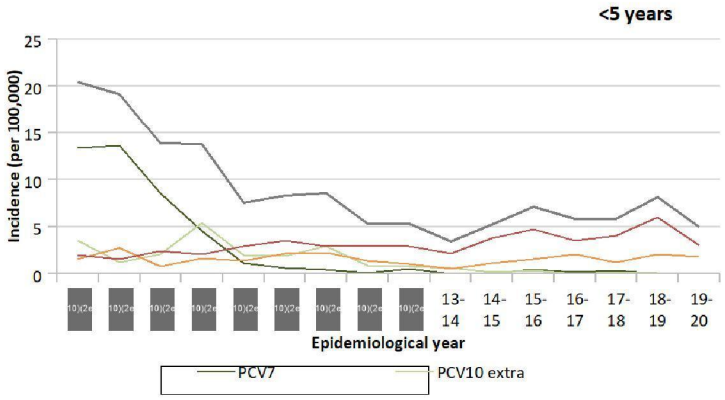

Figure 7.9.2 Incidence of invasive pneumococcal disease (IPD) in children <5 years of age by serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes, non-PCV13 serotypes and all serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)

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 2019-2020, data of national surveillance have been used.

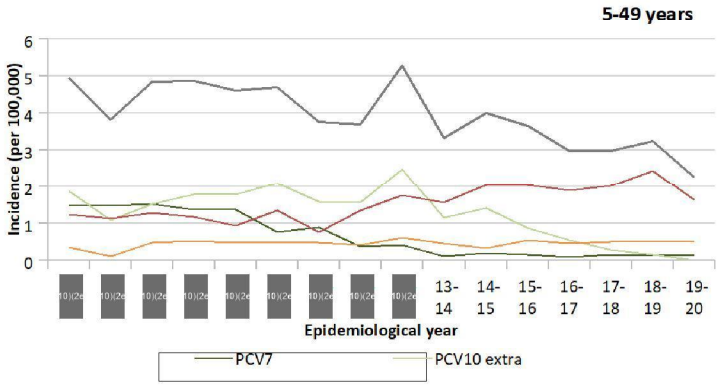

Figure 7.9.3 Incidence of invasive pneumococcal disease (IPD) in persons 5-49 years of age by serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes, non-PCV13 serotypes and all serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)

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

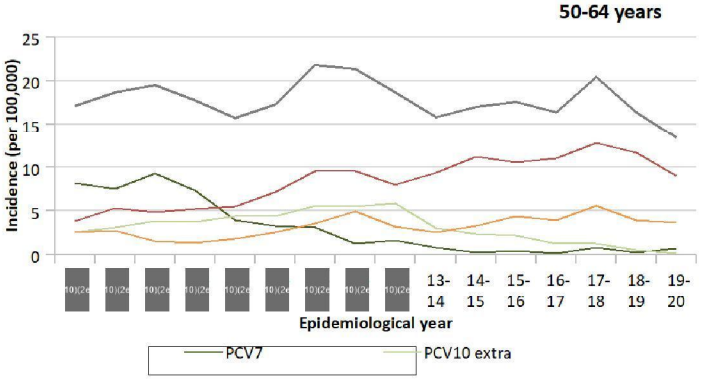

Figure 7.9.4 Incidence of invasive pneumococcal disease (IPD) in persons 50-64 years of age by serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes, non-PCV13 serotypes and all serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)
PCV7 was introduced in June 2006 and PCV10 in May 2011. Sentinel surveillance data have been used and extrapolated to the Dutch population.

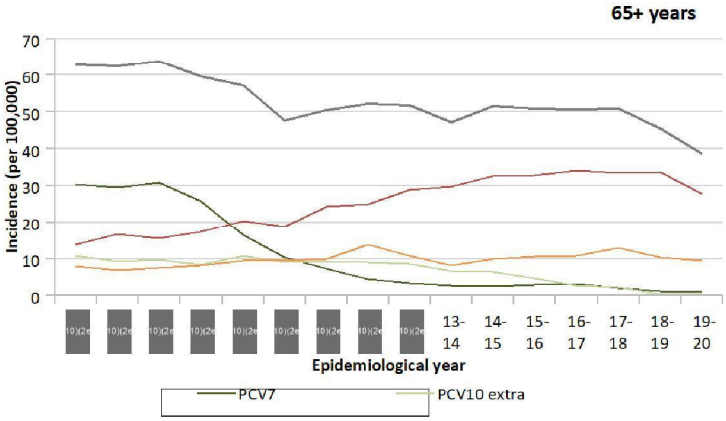

Figure 7.9.5 Incidence of invasive pneumococcal disease (IPD) in persons aged 65 years or more by serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes, non-PCV13 serotypes and all serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)
PCV7 was introduced in June 2006 and PCV10 in May 2011. Sentinel surveillance data have been used and extrapolated to the Dutch population.

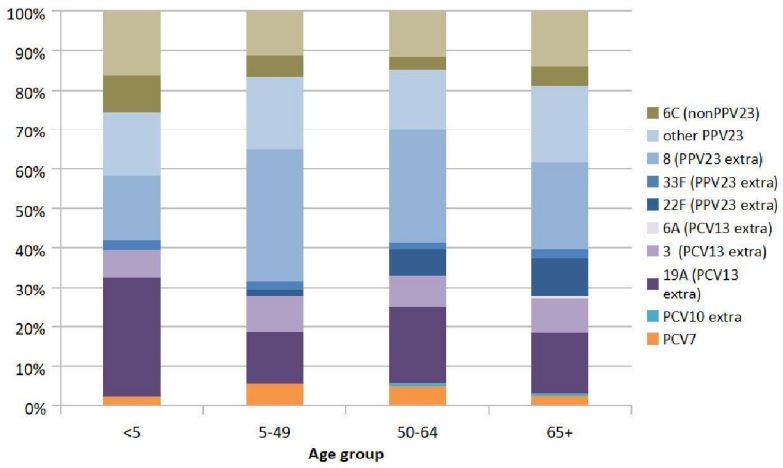

Figure 7.9.6 Distribution of serotypes causing invasive pneumococcal disease (IPD) in epidemiological year 2019/2020

For children <5 years, data of the national surveillance system have been used. For other age groups, sentinel surveillance data have been used.

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	?
2019	3	14	PCV10	2	None

7.9.5 *Epidemiology*

7.9.5.1 Overall

While the overall IPD incidence has been quite stable over time since 2004/2005 with an average incidence of 15.2 per 100,000 per year (range: 13.4 to 16.7 per 100,000 per year), the incidence in epidemiological year 2019/2020 (June to May) decreased to 11.9 per 100,000 per year. The number of cases suddenly dropped by 80% in April and May 2020 compared with the 5-year moving average (Figure 7.9.1). This is most likely related to the COVID-19 measures (e.g. social distancing and school closures) that were issued mid-March, most probably causing less transmission of pneumococci and influencing health care seeking behaviour. This drop in cases was seen in all age groups and affects the age-specific time trends described below.

7.9.5.2 Children <5 years of age (Figure 7.9.2)

In the epidemiological year 2019/2020, 43 IPD cases were reported in children <5 years of age, resulting in an incidence of 5.0 per 100,000 per year. 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. In 2019/2020, the incidence decreased and was significantly lower than in 2018/2019 (39% reduction), which is probably (partly) caused by the COVID-19 measures (see section 7.9.3.1). The incidence in 2019/2020 was 75% lower than before the introduction of PCV7 and 41% lower than before PCV10 introduction.

In 2019/2020, there was only one IPD case caused by a serotype included in PCV10. 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, although in 2019/2020 the non-PCV10 incidence decreased, again presumably partly caused by the COVID-19 measures. In 2019/2020, there were 16 IPD cases (37%; 1.8 per 100,000 per year) caused by the three additional serotypes included in PCV13 (serotype 3, 6A and 19A, see Table 7.9.1). This incidence has been stable in the last four years. In 2019/2020, the most common serotypes were 19A (13 cases), 8 (7 cases) and 6C (4 cases) causing 56% of all cases in this age group (Figure 7.9.6).

7.9.5.3 Persons aged 5-49 years (Figure 7.9.3)

In the epidemiological year 2019/2020, 54 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 2.3 per 100,000 per year. The incidence in this age group has decreased slightly over time since the introduction of PCV7. In 2019/2020, the incidence decreased significantly compared with 2018/2019 (30% reduction), presumably partly caused by the COVID-19 measures (see section 7.9.3.1).
IPD incidence due to serotypes included in PCV10 has decreased substantially compared to the incidence before introduction of PCV in 2006, dropping from 3.0 to 0.1 per 100,000 per year in 2019/2020. However, a significant increase has been observed in IPD incidence caused by serotypes not included in PCV10, rising from 1.5 to 2.1 per 100,000 per year in 2019/2020. In 2019/2020, the most common serotypes were 8 (18 cases) and 19A (7 cases) causing 46% of all cases in this age group (Figure 7.9.6).

7.9.5.4 Persons aged 50-64 years (Figure 7.9.4)

In the epidemiological year 2019/2020, 121 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 13.4 per 100,000 per year. The incidence in this age group has been quite stable over time, fluctuating around ~18 per 100,000 per year. Although in 2019/2020, a decrease was seen, presumably caused by the COVID-19 measures (see section 7.9.3.1).
IPD incidence due to serotypes included in PCV10 has decreased substantially compared to the incidence before introduction of PCV in 2006, from 10.7 to less than 1.0 per 100,000 per year in 2019/2020. However, a significant increase has been seen in IPD incidence caused by serotypes not included in PCV10, from 7.2 to 12.6 per 100,000 per year in 2019/2020. In 2019/2020, the most common serotypes were 8 (35 cases), 19A (23 cases), and 3 (10 cases) causing 56% of all cases in this age group (Figure 7.9.6).

7.9.5.5 Persons aged 65 years or more (Figure 7.9.5)

In the epidemiological year 2019/2020, 320 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 38.6 per 100,000 per year. The incidence in this age group decreased in the first years after PCV7 introduction and has remained stable over the past 10 years. However, a significant decrease of 15% was observed in

2019/2020 compared with the year before, presumably partly caused by the COVID-19 measures (see section 7.9.3.1).
IPD incidence due to serotypes included in PCV10 has decreased substantially compared to the incidence before introduction of PCV in 2006, from 40.2 to less than 1.5 per 100,000 per year in 2019/2020 (97% reduction). However, a significant increase has been seen in IPD incidence caused by serotypes not included in PCV10, from 22.5 to 37.4 per 100,000 per year in 2019/2020. IPD incidence due to serotypes included in PCV13 but not PCV10 has increased by 30% compared to the incidence before introduction of PCV in 2006. IPD due to serotypes not included in PCV13 has increased by 83%. In 2019/2020, 171 (53%) 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 in 2004/2005 to 20.6 per 100,000 per year in 2019/2020. In 2019/2020, the most common serotypes were 8 (70 cases), 19A (49 cases), and 22F (31 cases) causing 47% of all cases in this age group (Figure 7.9.6).
In 2020, PPV23 vaccination was planned to be offered to all 60-, 65-, 70- and 75-year-olds in the Netherlands. However, due to the COVID-19 pandemic, priority has been given to the oldest age groups. Therefore, in Autumn 2020 all 73-79 year olds will be offered PPV23 vaccination. It has not yet been decided which age groups will be targeted in 2021.

7.9.5.6 Vaccine failure

Since the introduction of PCV7, 44 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, 21 children (48%) 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, 33%). There was one vaccine failure case in 2019, vaccinated with PCV10.

7.9.5.7 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.
Nine of the 19 (47%) vaccine type IPD cases were vaccinated with at least two doses, as were 254 of the 284 (89%) non-vaccine type IPD cases. This resulted in a VE of 89% (95%CI 72-96%) for at least two doses of PCV10 compared with zero doses. The VE against serotype 19A (not covered by PCV10) was 48% (95%CI -20 to 78%). From these results, cross-protection of PCV10 against vaccine-related IPD including serotype 19A cannot be confirmed.

7.9.5.8 IPD mortality among children <5 years

From 2014 to May 2020, 347 IPD cases among children aged under five were reported nationally. For 235 cases (68%), the mortality status was known. Seventeen of the 235 cases (7%) died. These 17 cases all had non-vaccine type IPD (serotypes 8 (n=4), 3 (n=2), 12F (n=2), 6C

(n=2), 22F, 10A, 15C, 19A, 23A, 24F, 31). Fifteen cases were <2 years of age and four had known comorbidity.

7.9.6 *Pathogen*

In the period 2004-2016, capsular switches occured 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.

7.9.7 *Current/ongoing research at RIVM*

In older adults, pneumococcal disease is strongly associated with respiratory viral infections, but the impact of viruses on *Streptococcus pneumoniae* carriage prevalence and load remains poorly understood. Miellet et al. investigated the effects of influenza-like illness (ILI) on pneumococcal carriage in community-dwelling older adults by quantifying pneumococcal DNA with quantitative-PCRs in saliva samples, collected in the 2014/2015 influenza season from 232 individuals with ILI and 194 asymptomatic controls (Preprint on BioRivx:xxxxx). The prevalence of pneumococcus-positive samples was highest at onset of ILI (18%; 42/232) and lowest among controls (11%; 22/194), though these differences were not significant. Pneumococcal carriage was associated with exposure to young children and rhinovirus infection. When compared with carriers among controls, pneumococcal abundances were significantly higher at onset of ILI, and remained elevated beyond recovery from ILI. Finally, predicted pneumococcal abundances were highest in carriage events newly-detected after ILI compared with pre-existing carriage. Taken together, this study shows that ILI enhances pneumococcal colonization of the airways in older adults, and this effect persists beyond recovery from ILI.

7.9.8 *(Inter)national developments*

7.9.8.1 Carriage

Wouters et al assessed pneumococcal carriage in Belgium in children during/after the switch from PCV13 to PCV10 in 2015/2016 [1]. A total of 2,615 nasopharyngeal swabs from children (6–30 months old) attending day care were collected in three periods over 2016–2018. The overall pneumococcal carriage prevalence remained stable over the study period (76-80%). The proportion of non-PCV13 vaccine serotypes among carriers decreased over the study period from 95% in 2016 to 90% in 2017–2018. The proportion of PCV13-non-PCV10 vaccine serotypes increased from 1% in 2016 to 8% in 2017–2018. This increase was mainly due to an increase in serotype 19A carriage.

7.9.8.2 PCV10

Rinta-Kokko et al estimated the VE of PCV10 in children in Finland using three different study designs, namely a cohort study, nested case-control study and the indirect cohort design [2]. VE against PCV10 serotype IPD was 93% (87-97%), 98% (90-100%) and 100% (98-100%) for the three designs, respectively. The VE against PCV10-related serotypes ranged between 46 and 78% for the different study designs, and was not significant in any of the designs. VE against all IPD was estimated at 54% (24-71%) in the cohort study and at 61% (26-79%) in the case-control study.

Karppinen et al estimated the VE of PCV10 against respiratory tract infections in 424 children in a follow up study of the Finnish Invasive Pneumococcal disease vaccine trial, a cluster-randomised double-blind trial [3]. The children vaccinated with PCV10 had lower mean annual rates of respiratory tract infections than control children in the first two years of life. The VE was 12% (2-22%) against all respiratory tract infections, 23% (0-40%) against respiratory tract infections with acute otitis media and 10% (0-19%) against respiratory tract infections without acute otitis media.

7.9.8.3 PCV13

Yildirim et al assessed predictors of PCV13 vaccine failure, where vaccine failure was defined as diagnosis of IPD due to a vaccine serotype in a child who received age recommended doses [4]. During seven years, 37 (34%) vaccine failure cases were identified among a total of 296 IPD cases. Older age (>5 years), presenting with pneumonia and underlying comorbidity were predictors of vaccine failure.

Amin-Chowdhurry et al assessed clinical characteristics of patients with IPD caused by the emerging serotypes 8, 12F and 9N in England from 2014-2018 [5]. These three emerging serotypes are responsible for 38% of the IPD cases in England. Serotypes 8 and 12F were more likely to cause IPD in younger, healthier individuals and less likely to be fatal, while serotype 9N affected older adults with comorbidities and had higher cases fatality.

7.9.8.4 Pneumococcal pneumonia

Cassir et al reported an outbreak of pneumococcal pneumonia among shipyard workers in Marseille, France, from January to February 2020 [6]. A total of 37 cases were identified of which 18 were hospitalized including five in an intensive care unit. The cases presented several risk factors for pneumococcal disease including exposure to respiratory irritants (dust, solvent, metal fumes), smoking and viral coinfections. In addition, the workers lived and worked in crowded environments. Following the outbreak, a mass vaccination campaign with PPV23 was implemented for 4300 workers and crew members, of which 1460 were vaccinated. Pneumococcal outbreaks on shipyards have been described before in Singapore, Norway and Finland. Some European countries have recommendations for PPV23 vaccination for specific occupations like welders.

7.9.8.5 Schedule

Adebanjo et al showed that vaccine failure rates of PCV13 were higher in children <1 year receiving a 2+0 versus a 3+0 schedule (incidence rate ratio: 12.9; 4.1-40.4) [7]. Results for PCV7 were similar. There were no differences between schedules in children >= 1 year of age.

Cost-effectiveness

7.9.8.6 Children

Pugh et al. estimated the clinical and economic benefit of replacing PCV10 with PCV13 in three countries: Colombia, Finland, and The Netherlands [8]. Over a 5-year time period, a switch to a PCV13 program was estimated to reduce overall IPD among 0–2 year olds by

37.6% in Colombia, 32.9% in Finland, and 26% in The Netherlands. In adults > 65 years, decrease in overall IPD were estimated in Colombia (32.2%), Finland (15%), and The Netherlands (3.7%). For Colombia and Finland, the implementation of PCV13 would be cost saving. For the Netherlands the incremental costs per quality adjusted life-year (QALY) gained would be €28,260. Ansaldi et al. found similar results for Italy [9]; in this country PCV13 is already included in the National Immunization Program. The economic impact of changing the vaccination program from PCV13 to PCV10 in Italy were assessed. The incremental cost-effectiveness ratio (ICER) for PCV13 compared to PCV10 was €28,963 per QALY gained. Switching from PCV13 to PCV10 would increase the incidence of pneumococcal disease primarily linked to re-emergence of serotypes 3 and 19A. Both studies were performed by Pfizer Inc.

7.9.8.7 Adults

In 2018, the Dutch Health Council advised on elderly pneumococcal vaccination favouring the polysaccharide vaccine over the conjugated vaccine. This advice was based on a cost-effectiveness analysis showing favourable outcomes for the polysaccharide but not for the conjugated vaccine. Zeevat et al recalculated the cost-effectiveness using a longer time horizon and lower vaccine prices [10]. In this recalculation, also the conjugated vaccine becomes cost-effective; i.e. well below the threshold of €20,000 per QALY gained. This study received an unrestricted grant from Pfizer Inc.

Continued indirect effects provided by the childhood PCV13 program in the United States have decreased disease in the adult population, reducing the potential direct effects of vaccinating older adults. Stoecker et al evaluated the incremental cost-effectiveness of continuing to recommend PCV13 in series with PPV23 at age 65 compared to a strategy that only included a recommendation for PPV23 at this age [11]. In the base case scenario, continuing to recommend PCV13 at age 65 costs $561,682 per QALY gained. The costs per QALY have increased nearly 10-fold since the last analysis in 2014, when this recommendation was made by the ACIP. Therefore, according to the authors, routine PCV13 use among immunocompetent adults 65 years or older is to be discussed in a setting of fully realized PCV13 indirect effects.
Wateska et al. have published five economic evaluations of pneumococcal vaccination programs in US adults. In line with Stoecker et al she found that the current pneumococcal vaccination recommendations for US older people are economically unfavourable compared to an alternative strategy omitting PCV13 in the immunocompetent [12, 13]. In another study vaccinating high-risk individuals with PPV23/PCV13 proved to be the most favourable strategy, with $57,786/QALY gained [14]. In a fourth study the cost-effectiveness of a vaccine uptake improvement program among the US black and general population cohorts aged 50 years with high-risk conditions was assessed [15]. In both black and general population cohorts, an uptake improvement program for current vaccination recommendations was favoured, costing $48,621 per QALY gained in black populations ($54,929/QALY in the general population) compared to current recommendations without a program. A fifth study focused on

underserved minority populations [16]. Prior analyses suggest routine pneumococcal vaccination at age 50 could be considered, which could disproportionately benefit underserved populations. However, the current CDC recommendations (both vaccines for the immunocompromised, polysaccharide vaccine for other high-risk conditions) were economically favourable as vaccinating all 50-year-olds would not be cost-effective at >$250,000 per QALY gained.

7.9.8.8 Pneumococcal vaccines in development

Pfizer is developing a 20-valent pneumococcal conjugate vaccine (20vPnC) 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. 20vPnC includes the 13 serotypes contained in PCV13 (see Table 7.9.1) plus 7 additional serotypes (8, 10A, 11A, 12F, 15BC, 22F and 33F). These 20 serotypes are currently responsible for the majority of pneumococcal disease in adults and the seven additional serotypes are global causes of IPD, and are associated with high case-fatality rates, antibiotic resistance, and/or meningitis.
Three phase III trials have been completed. One of the studies (NCT03760146) evaluated the safety and immunogenicity of 20vPnC compared with PCV13 and PPV23 in 3880 adults aged 18 years or older who were not previously vaccinated against pneumococcal disease [17]. This study showed non-inferiority at one month after vaccination for all serotypes in common with PCV13 and for six of the seven additional serotypes when compared to the PPV23 in adults of 60 years and older; one of the new seven serotypes missed non-inferiority criteria by a small margin. Antibody levels in adults 18-59 years old were non-inferior compared to those in 60-64 years old for all 20 serotypes. The safety and tolerability of 20vPnC was comparable to licensed pneumococcal vaccines. Clinical development for use in paediatric populations is in progress. The adult indication of 20vPnC will be submitted to the FDA by the end 2020.

MSD is developing a 15-valent pneumococcal conjugate vaccine (V114) including serotypes 22F and 23F in addition to the serotypes included in PCV13. A phase II trial compared V114 with PCV13 in 1,050 healthy infants who were vaccinated at two, four, six and 12-15 months of age [18]. The study showed that the percentage of subjects who achieved the WHO-accepted threshold of protection (IgG≥0.35 mcg/mL) with V114 was non-inferior to the percentage seen with PCV13 for the 13 serotypes shared between the two vaccines. For serotype 3, the percentage of subjects who achieved this threshold was higher for V114 (96.0% for lot 1; 94.1% for lot 2) compared with PCV13 (71.8%). For the two serotypes not included in PCV13, the percentage of subjects who achieved the threshold was above 98% for serotype 22F and above 87% for serotype 33F. Results were consistent between the two lots of V114 studied. The adverse event profile for V114 was found to be comparable to PCV13. The most commonly reported adverse events were injection site reactions, the majority of which were mild to moderate in severity and of short duration. 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 IPD.

Both vaccines have received a Breakthrough Therapy Designation from the FDA. This designation is designed to expedite the development and review of drugs and vaccines that are intended to treat or prevent serious conditions and for which preliminary clinical evidence indicates that the drug or vaccine may demonstrate substantial improvement over available therapy on a clinically significant endpoint.

In addition to PCVs, several other vaccine concepts are currently being tested in clinical development programs including a new generation (killed) whole cell pneumococcal vaccine based on an unencapsulated serotype that allows the expression of many bacterial antigens. These vaccines are currently being tested in phase I/II trials. Another concept is pneumococcal protein (PnPs) vaccines with proteins that are universally expressed among serotypes; these are also being tested in phase I/II trials. Both vaccine types may induce broader protection while they are easier to manufacture and less expensive than PCVs.

7.9.9 *Literature*

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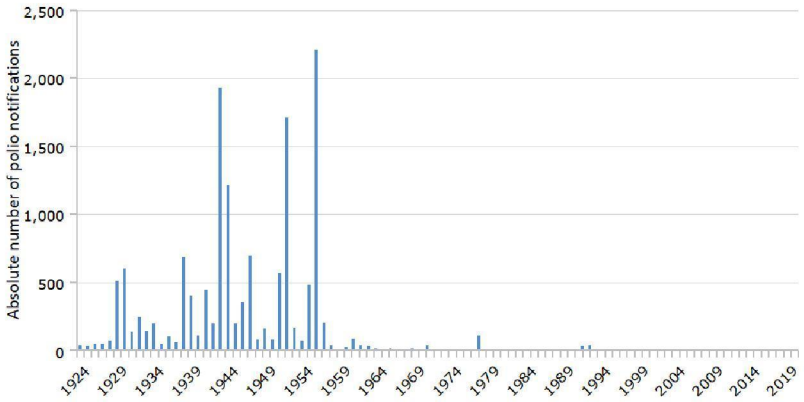
7.10 Poliomyelitis

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

7.10.3 *Key points*

- In 2019 and 2020 up to July 1st, no cases of poliomyelitis were reported in the Netherlands, including the Caribbean Netherlands.
- In an historic announcement on World Polio Day (24 October 2019), an independent commission of experts concluded that wild poliovirus type 3 (WPV3) has been eradicated worldwide. Two of three wildtype polioviruses (i.e. WPV2 and WPV3) have been declared eradicated.
- In 2019-2020, poliovirus remained endemic in three countries; Nigeria, Afghanistan and Pakistan.
- On 21 Augustus 2019 Nigeria, and thus the Afro region, was free of wildtype poliovirus for 3 consecutive years. The certification process to declare the 5th of 6 WHO regions wildtype polio free is in progress and will likely be finalized in 2020.
- Worldwide, the number of circulating vaccine derived poliovirus (cVDPV) was higher in 2019 (368) than in 2018 (105).
- To sustain a world free of all polioviruses, the Global Polio Eradication Initiative (GPEI) has released a Polio Endgame Strategy 2019-2023 in 2019.

7.10.4 *Tables and figures*



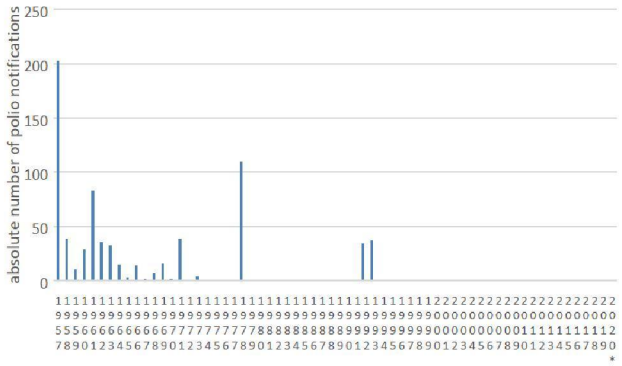


Figure 7.10.1 Notifications of poliomyelitis in the Netherlands from 1924-2020 and zoomed in on 1957-2020* (lower part)*
*for 2020, reports up to July 1st were included

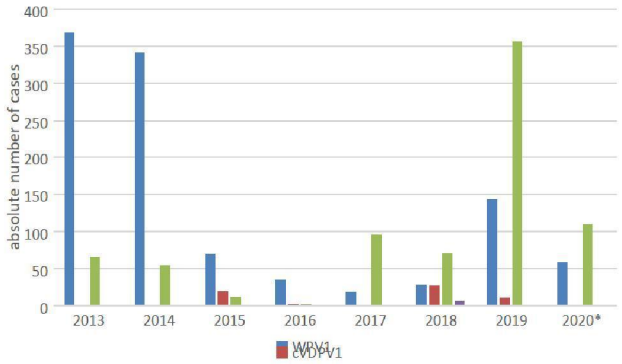


Figure 7.10.2 Total number of global polio cases 2013-2020 as reported to WHO HQ. For 2020, data up to May 20 were included.*

7.10.5 *Epidemiology & pathogen*

In 2019 and 2020 up to July 1st, 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.

7.10.6 *Research*

The National Polio Laboratory (NPL) at the RIVM participates in several projects of the WHO Global Polio Laboratory Network (GPLN), including development of sensitive methods for direct poliovirus detection in clinical samples and the feasibility of Next Generation Sequencing

methods to detect poliovirus sequences in sewage samples and samples from immunocompromised children.
Additionally, the NPL had piloted an Environmental Surveillance Quality Assurance program to support the GPLN and the Environmental Surveillance expansion plan. In 2019-2020, 30 laboratories have participated in ESQA pilot 3 and the ESQA is awaiting full implementation in the GPLN QA program. In cooperation with the immune-surveillance department at the RIVM, the NPL is developing new serological assays that can be used outside of GAPIII containment Additionally, the NPL RIVM participates in the validation of new poliovirus strains (S19 strains), including type 2, that can be used outside of GAPIII containment for use in the poliovirus neutralization assay.

7.10.7 *International developments*

In 2019-2020, WHO classified three countries – Nigeria, Afghanistan and Pakistan as polio-endemic countries. Importation of polio into non-endemic countries was not observed. From 2016 onwards, no WPV cases were notified in Nigeria. As a result, Nigeria, and thus the Afro region, was free of wildtype poliovirus for 3 consecutive years. The certification process to declare the 5th of 6 WHO regions wildtype polio free is in progress and will likely be finalized in 2020.
In Afghanistan and Pakistan, a combined total of 176 WPV1 cases were notified in 2019, and 59 WPV1 cases in 2020 up to May 20 [1]. In 2019, 3 WPV1 were detected in Iran's environmental surveillance. Fortunately, this did not result in ongoing transmission and up to July 1, 2020 no cases were reported in Iran.
The number of circulating vaccine derived poliovirus (cVDPV) was higher in 2019 (368) compared to 2018 (105) and mainly concerned cVDPV2. (Figure 7.10.2). Therefore there has been a higher demand of mOPV2, a WHO-prequalified vaccine with the same operational characteristics as bivalent oral polio vaccine (bOPV). This high demand has even threatened the stock of this vaccine. The WHO advised that all countries should destroy the materials containing poliovirus type 2, and provide at least one inactivated polio vaccine (IPV) in their routine vaccination schedule. In May 2019 WHO announced that all countries worldwide had introduced at least 1 IPV dose [2]. Polio eradication progress is hampered by the Covid19 pandemic.
The current approach to fight cVDPV2 outbreaks is by using mOPV2, i.e. fighting fire with fire. The newly developed newOPV2 (nOPV2) strain is in an Emergency Use Listing procedure (EUL) that would allow use of this (presumably) safer vaccine in regions where cVDPV2 outbreaks are occurring. The NPL RIVM participates in the development of detection methods for this specific strain in environmental surveillance.
To sustain a world free of all polioviruses, the Global Polio Eradication Initiative (GPEI) has released a Polio Endgame Strategy 2019-2023 in 2019 [3]. 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 [4].

7.10.8 *Literature*

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3. Global Polio Eradication Initiative. Polio Endgame Strategy 2019-2023. GPEI 2019. http://polioeradication.org/wp-content/uploads/2019/05/polio-endgame-strategy-2019-2023.pdf
4. WHO. Roadmap for assessment of nOPV2 manufactured by Biofarma under the EUL procedure. https://www.who.int/medicines/news/2020/roadmap-assessment-nOPV2.pdf?ua=1

7.11 Rubella

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

7.11.3 *Key points*

- In 2019 and the first six months of 2020, no rubella cases were reported in The Netherlands.
- Results from the 2016/2017 PIENTER study indicate high overall seroprevalence of protective antibodies in 95% of the general population.
- In the PIENTER study the highest susceptibility was seen among children within the orthodox Protestant community, born after the last rubella epidemic in 2005, indicating an outbreak can be expected after introduction of rubella virus in this community.
- Across Europe, the number of rubella cases continued to decline in 2019.

7.11.4 *Tables and figures*

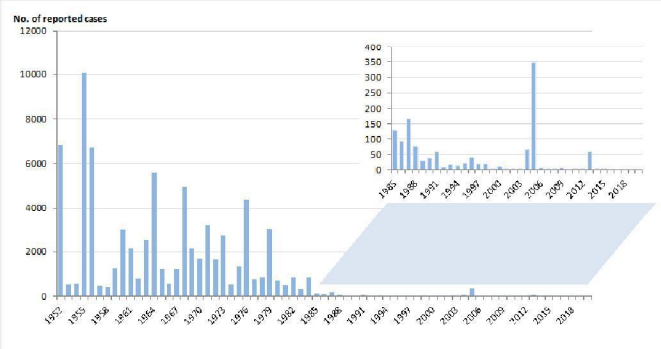

Figure 7.11.1 Total annual reported rubella cases in The Netherlands, from 1952 – 2018

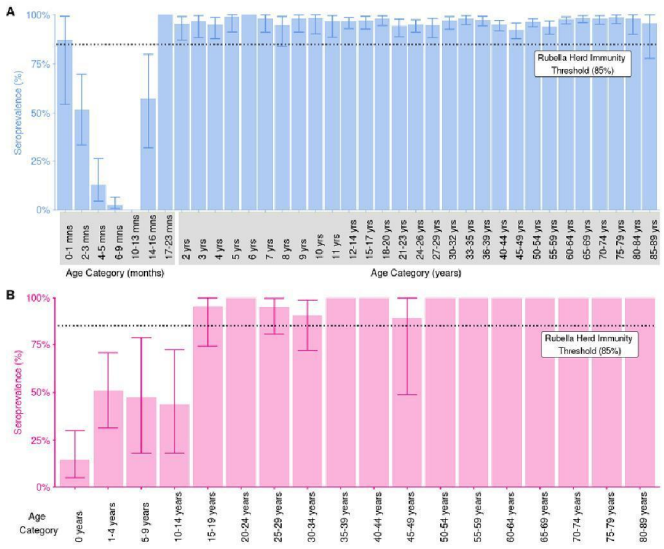

Figure 7.11.2 Seroprevalence of rubella IgG antibodies (cut-off is ≥10 IU/ml) by age category in The Netherlands, 2016/17. Panel A: Results for the general Dutch Population (N=5,146); Panel B: Results for the Protestant Orthodox Reformed community (N=1,355).

7.11.5 *Epidemiology*

Throughout 2019 and during the first six months of 2020, no new rubella cases were reported in The Netherlands. The last case of rubella was reported in 2015 (Figure 7.11.1).

7.11.6 *Research*

Seroepidemiology is an important tool to monitor the (long-term) effects of the national immunization programme (NIP) on population level immunity. In The Netherlands a population-based study is performed every ten years (1995/1996-2006/2007-2016/2017) to assess immunity within the Dutch population (0-79/89 years of age), and among the socio-geographically clustered Protestant orthodox reformed community, who often refuse vaccination. The third PIENTER study (PIENTER 3) was conducted during 2016 and 2017, and included over 7000 participants. Serum samples were analysed by a bead-based multiplex immunoassay.

Immunity against rubella was assessed and protective immunity defined as a concentration of rubella IgG ≥10 IU/ml [1]. Preliminary analyses indicate that the Dutch population is well protected against rubella, with a high overall seroprevalence of protective antibodies of 94.8% (95% CI 94.0-95.5%). Highest susceptibility was seen in children under 14 months of age, prior to the administration of the 1er dose of a rubella containing vaccine (Figure 7.11.2A.)

Analyses indicated that susceptibility was higher among orthodox reformed individuals than in the general Dutch population, with an overall seroprevalence of rubella protective antibodies of 86.6% (95% CI 80.7-91.2%). The highest susceptibility was seen among children under 12 years of age within the orthodox Protestant community, born after the last rubella epidemic in 2005 (Figure 7.11.2B). This situation requires ongoing sensitive surveillance monitoring, as with low rubella incidence within The Netherlands a considerable pool of rubella susceptible individuals will accumulate. ~~*This group could be at risk of a new outbreak due to imported cases of rubella, as internationally levels of rubella vaccination coverage and incidence vary. This is particularly concerning for women and girls of child bearing age within this community, due to the risk of Congenital Rubella Syndrome (CRS), of which there was a high burden as a result of the last large epidemic.*~~

7.11.7 *International developments*

In Europe, reported rubella cases declined from 1326 in 2016, to 579 in 2018. In 2019, the same tendency was observed with 389 rubella cases reported by 9 EU/EEA Member States. Nineteen countries reported no cases. The highest numbers of cases were reported by Poland (292), Germany (57) and Italy (22) [2, 3]. The data from Poland should be interpreted with caution as rubella is reported based on clinical symptoms and only 4 of 292 cases (1%) was laboratory confirmed [3].

Further afield, rubella-containing vaccine has been introduced nationwide in 173 of 194 WHO Member States as of the start of 2020, and global coverage is estimated to be 71% [4]

A meta-analysis of 42 studies found no evidence that rubella-containing vaccines caused congenital rubella syndrome (CRS) in infants born to mothers inadvertently vaccinated against rubella during early pregnancy. The authors found that CRS was effectively prevented by vaccination, and thus support continued rubella vaccination efforts. The data confirmed previous recommendations that inadvertent vaccination during pregnancy is not an indication for termination [5].

A study in Japan found evidence for decreased fertility following a large outbreak of Rubella from 2012-2014. Fertility rates were found to decline after each geographical epidemic peak, and were also strongly associated with the frequency of online google searches for "rubella" during the epidemic. As the overall number of cases in Japan was relatively small and online search activity considerably elevated, the authors proposed that reduced fertility was associated not with stillbirths or miscarriages, but due to perceived increased risk of CRS during the outbreak and subsequent voluntary pregnancy delays [6].

7.11.8 *Literature*

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3. European Centre for Disease Prevention and Control, Monthly Measles and Rubella monitoring report – February 2020. 2019, ECDC: Stockholm.
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6. Mizumoto, K. and G. Chowell, Temporary Fertility Decline after Large Rubella Outbreak, Japan. Emerg Infect Dis, 2020. 26(6): p. 1122-1129.

*RIVM publication.

7.12 Tetanus

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

7.12.3 *Key points*

- In 2019, no cases of tetanus were notified.
- In 2020, up to June 1st, two cases were reported, one elderly women who was not eligible for routine vaccination and one unvaccinated 12-year-old.
- In a European seroprevalence study among 40-59-year-olds, seroprotection levels for tetanus were sufficient with only very few sera lacking basic immunity. In the Dutch serum samples, based on Pienter3 participants, only 0.3% and 5.2% had anti-tetanus antibody levels <0.01 IU/ml and <0.1 IU/ml, respectively.

7.12.4 *Tables and figures*

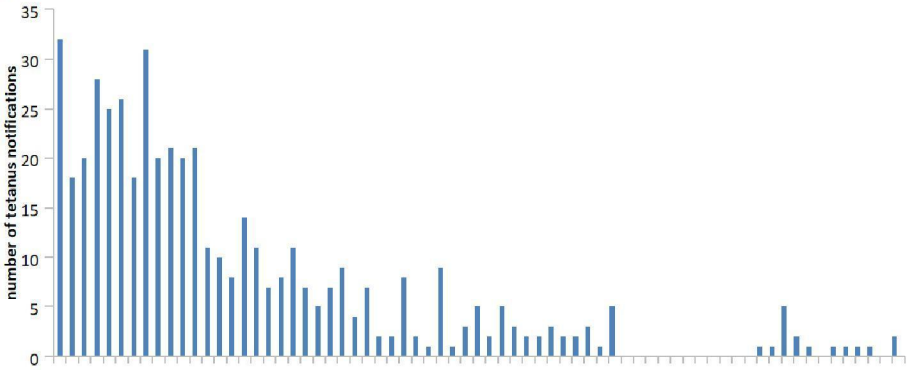

*Figure 7.12.1. Reported cases of tetanus in the Netherlands by year, 1952-2020^*
*Between 1999 and 2009 tetanus was not notifiable.
^ For 2020, notification up to June 1st were counted.

7.12.5 *Epidemiology*

In 2019, no cases of tetanus were reported. Up to June 2020, two cases were reported. One case concerned a woman, born in 1943 and therefore not eligible for the NIP. She contracted a wound after falling off her bike. For post exposure prophylaxis, she received tetanus toxoid but no tetanus immunoglobulins although the latter is recommended. She was hospitalized with clinical signs of tetanus. No *Clostridium tetani* was cultured from the wound.
The second case concerned an unvaccinated 12 year old boy, who contracted a headwound due to a slap with a branch. Within several days he developed clear signs of tetanus: neck stiffness, cramps of the facial muscles including a lockjaw, and of the chest musculature. He was hospitalized and due to difficulties with breathing he was transferred to the intensive care unit. After several weeks of severe illness he recovered. *Clostridium tetani* was cultured from the wound, although no tetanus toxin was found.

7.1.6 *International developments*

Within the framework of the EUPertstrain group, a collaboration between European experts on whooping cough, a seroprevalence study in European countries for pertussis, diphtheria and tetanus antibody levels in the 40-60 years age groups has been conducted by the RIVM and funded by ECDC [1]. 18 European countries have participated and collected the requested sera (around 500). Measurement of the antibody levels against pertussis toxin, diphtheria toxoid and tetanus toxin with the MIA has been completed last year establishing a final database of around 30,000 results. The seroprotection levels for tetanus were sufficient with only very few sera lacking basic immunity. The proportion of sera with levels below 0.01 IU/mL ranged from 0-1.2%, apart from Greece (2.8%). For the total cohort, seven countries were considered as fully protected. The protective level of 0.1 IU/mL was reached in more than 90% of the sera in all countries, apart from Greece (79%) and Ireland (83%). In the other 16 countries the proportion of sera with unprotected levels (<0.1 IU/mL) ranged from 0.4% to 8.2%. In the Dutch serum sample, based on Pienter 3 participants, 0.3% and 5.2% had anti-tetanus antibody levels <0.01 IU/ml and <0.1 IU/ml, respectively.

7.1.7 *Literature*

1. *G. Berbers, P. van Gageldonk, J. van de Kassteele, U. Wiedermann, I. Desombere et al. Widespread ciriculation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries. Nature research 2020, Preprint 2020. DOI 10.21203/rs-35858/v1.

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

T.M. Schurink-van 't Klooster, E.A. van Lier, E. Vos, H. Pasmans, K. Hulshof, J. van Slobbe, F. Rooyer

8.1 Key points

- In general, vaccination coverage in the Dutch overseas territories, including Caribbean Netherlands (i.e., Bonaire, St. Eustatius and Saba) is high.
- In 2019, no vaccine preventable diseases were reported on Bonaire and Saba.
- Findings from the Health Study Caribbean Netherlands indicate that HPV seroprevalence was high among individuals aged ≥15 years (34%), with over half of them being seropositive for ≥2 high-risk HPV types. Seroprevalence was substantial higher in women (51%) than men (18%), predominantly peaking in women aged 20-59 years. These data corroborate the decision regarding introduction of a sex-neutral HPV-vaccination program and the relevance for considering a population-based cervical cancer screening program in Caribbean Netherlands.

8.2 Tables and figures

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

	Aruba	Bonaire	Curaçao	Saba	St, Eustatius	St. Maarten
Newborns (2 years)						
Number in cohort 2017	*	*218*	*	*25*	*32*	*
Number DTaP-IPV-Hib-HBV	*	199	*	25	26	*
% DTaP-IPV-Hib-HBV	*	91,3%	*	100%	81,3%	*
Number HBV	*	n.a.	n.a.	n.a.	n.a.	*
% HBV	*	n.a.	n.a.	n.a.	n.a.	*
Number Polio	n.a.	n.a.	*	n.a.	n.a.	n.a.
% Polio	n.a.	n.a.	*	n.a.	n.a.	n.a.
Number Pneu	*	199	*	25	26	*
% Pneu	*	91,3%	*	100%	81,3%	*
Number MMR1	*	207	*	25	23	*
% MMR1	*	95,0%	*	100%	71,9%	*
Number MMR2	n.a.	n.a.	*	n.a.	n.a.	n.a.
% MMR2	n.a.	n.a.	*	n.a.	n.a.	n.a.
Number Men C	n.a.	204	n.a.	24	23	n.a.
% Men C	n.a.	93,6%	n.a.	96,0%	71,9%	n.a.
Toddlers (5 years)						
Number in cohort 2014	*	*	*	*22*	*37*	*
Number DTaP-IPV	*	*	*	22	30	*
% DTaP-IPV	*	*	*	100%	81,1%	*
Aantal MMR2	*	n.a.	n.a.	22	30	*
% MMR2	*	n.a.	n.a.	100%	81,1%	*

Schoolchildren (10 years)						
Number in cohort 2009	*	*	*	*15*	*48*	*
Number DTP	*	*	*	11	42	*
% DTP	*	*	*	[c] 73,3%	87,5%	*
Number MMR2	*	*	n.a.	13	n.a.	*
% MMR2	*	*	n.a.	[c] 86,7%	n.a.	*
Adolescent girls (10 years)						
Number in cohort 2009	*	*	*	*<10*	*27*	*
Number HPV	*	*	*	<10	21	*
% HPV	*	*	*	[c] 50,0%	77,8%	*

*Unknown because of research technical issues or not available yet due to special circumstances concerning the corona crisis.

[a] The registration systems in Caribbean Netherlands are not connected to the national population register, therefore, 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 can therefore in reality be higher 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] Interim vaccination coverage: the vaccination is linked to school year and not to birth year; for a part of these children vaccination will be offered in 2020.

Table 8.2 Number of reports of NIP-diseases in Caribbean Netherlands, 2017-2019

	Aruba	Bonaire	Curaçao	Saba	St. Eustatius	St. Maarten
Diphtheria						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
***Haemophilus influenzae* type b**						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Measles						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Meningococcal disease						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Mumps						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Pertussis						
Number of reports in 2017	*	2	*	0	*	*
Number of reports in 2018	*	1	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Pneumococcal disease						
Number of reports in 2017	*	0	*	0	*	*

Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Poliomyelitis						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Rubella						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Tetanus						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*

*Not available yet due to special circumstances concerning the corona crisis.

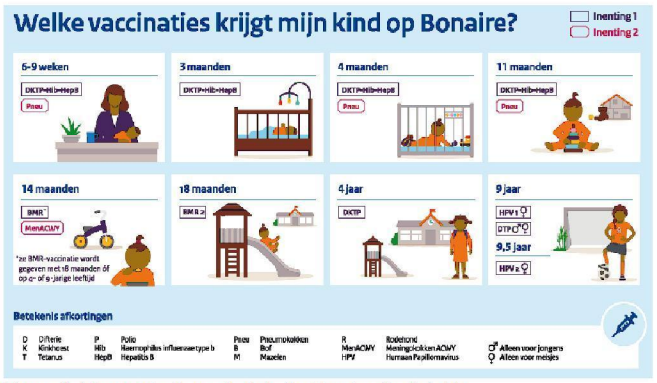

Figure 8.1 Immunisation schedule for Bonaire (in Dutch)

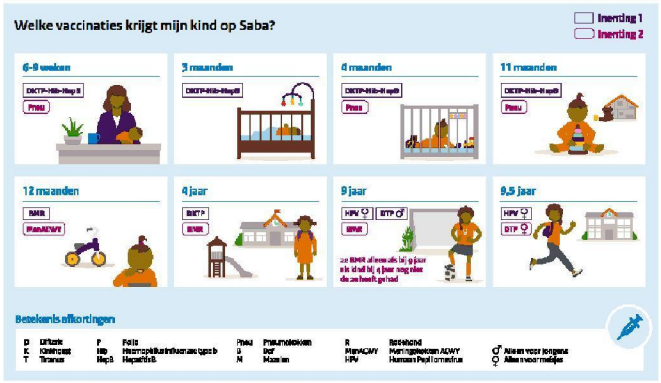

Figure 8.2 Immunisation schedule for Saba (in Dutch)

Vaccinatieschema			
Leeftijden	Vaccinatie 1	Vaccinatie 2	Vaccinatie 3
2 maanden (= 7 - 9 weken)	DKT 1 + HepB 1+ Hib 1	Polio 1 (IPV)	
3 ½ maanden	DKT 2 + HepB 2+ Hib 2	Polio 2 (bOPV)	Pneu 1 (10 valent)
5 maanden	DKT 3 + HepB 3+ Hib 3	Polio 3 (bOPV)	Pneu 2 (10 valent)
vanaf 12 maanden	BMR 1		Pneu 3 (10 valent)
15 maanden	DKT 4 + Hib 4 + HepB 4	Polio 4 (bOPV)	BMR 2
4 jaar	DT 1 (pediatric)	Polio 5 (bOPV)	
10 jaar	dT 2 (adult)		

Betekenis afkortingen

DKT	Difterie-Kinkhoest-Tetanus
DT	Difterie-Tetanus
dT	difterie-Tetanus (adult concentration)
HepB	Hepatitis B
Hib	Haemophilus influenzae type b
IPV	Inactivated Polio Vaccin
bOPV	bivalent Oral Polio Vaccin
BMR	Bof Mazelen Rubella
Pneu	Pneumokokken vaccin (PCV 10 valent)

Figure 8.3 Immunisation schedule for Curaçao

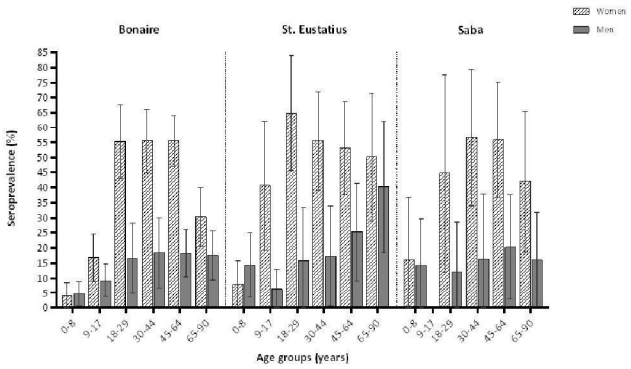

Figure 8.4 Age-specific seroprevalence (%) (with 95% confidence intervals) of any high-risk type human papillomavirus (HPV) IgG-antibodies in the general population of Bonaire, St. Eustatius and Saba, 2017, by sex

8.3 Immunisation schedules

Immunisation schedules in Caribbean Netherlands were presented in Figures 8.1-8.3.

8.4 Vaccination coverage

Table 8.1 presents the vaccination coverage in the Caribbean part of the Netherlands. Due to the special circumstances concerning the corona crisis, for the islands of Curaçao, Aruba and Sint Maarten it was not possible to provide timely data on the vaccination coverage. For research-technical reasons, not all data on vaccination coverage for Bonaire could be included in this report this year. However, there are no indications that there are any major changes in vaccination coverage compared to last year.

In general, vaccination coverage in the Caribbean part of the Netherlands is high. However, due to differences in target groups and vaccination schedules, data on vaccination coverage are not always easy to compare. The method for determining the vaccination coverage, as used in this chapter, gives often an underestimation for schoolchildren in this area, as vaccinations are usually offered per school year, regardless of a child's year of birth. In that case, the age limits of 5 and 10 years are not always met.

8.5 Epidemiology of diseases included in the NIP

Table 8.2 shows the number of reports of NIP-diseases in Caribbean Netherlands in 2017 to 2019.

8.5.3 *Epidemiology in Bonaire*

There have been a few cases of pertussis reported in 2017 and 2018 in Bonaire. In 2019 no cases of pertussis were reported.

8.5.4 *Epidemiology in Saba*

In the winter of 2019-2020, more people than usual were ill with flu-like symptoms, several dozen contacted the GPs for this. Diagnosis was conducted in a few people, in which Influenza A H1N1 was found.

8.6 Research

8.6.3 *Health Study Caribbean Netherlands: HPV seroprevalence and risk factors in Caribbean Netherlands*

Incidence and mortality of human papillomavirus (HPV)-related cancers differs geographically, with high rates in Caribbean countries. Seroepidemiological data provide information on lifetime cumulative HPV exposure and contributing risk factors, but this has not been available yet for Caribbean Netherlands. By means of the Health Study Caribbean Netherlands, a cross-sectional population-based serosurveillance study conducted in 2017, we aimed to estimate the seroprevalence in this (recently girls-only HPV-vaccinated) population (n=1,823, 0-90 years), and to identify risk factors for seropositivity among persons unvaccinated aged ≥15 years who ever had sex (n = 1,080). Blood samples were tested for seven high-risk HPV-type-specific IgG-antibodies (HPV16, 18, 31, 33, 45, 52, 58) using a viral-like particles-based multiplex-immunoassay.

Our findings indicate that seropositivity was high among individuals aged ≥15 years (34% (95% confidence interval 30.8-37.3)), with over half of them being seropositive for ≥2 high-risk HPV types, and HPV16 and 52 being most prevalent (13%). Seroprevalence was substantial higher in women (51%) than men (18%), predominantly peaking in women aged 20-59 years, and was highest on St. Eustatius (38%) (Figure 8.4). In addition to age group 25-34 years and female sex, sexual risk factors were associated with HPV-seropositivity, such as a higher number of lifetime partners and a history of sexual transmitted infection(s). Taken together, in accordance with the Caribbean region, seroprevalence of multiple hr-HPV types was high in Caribbean Netherlands. These data corroborate the decision regarding introduction of a sex-neutral HPV-vaccination program and the relevance for considering a population-based cervical cancer screening program.

8.7 Literature

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9. Future NIP candidates

9.1 Hepatitis A

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

9.1.3 *Key points*

- In 2019, the number of reported hepatitis A cases (n=164) slightly decreased compared to 2018 (n=188). Two new strains caused outbreaks among men who have sex with men (MSM).
- The number of cases in 2019 remains higher compared to 2011-2016 (80-125 cases).
- About two-third of the cases is 20 years or older.
- Forty-one per cent of the Dutch cases were reported to be travel-related, with Morocco reported for almost half of these cases.

9.1.4 *Tables and figures*

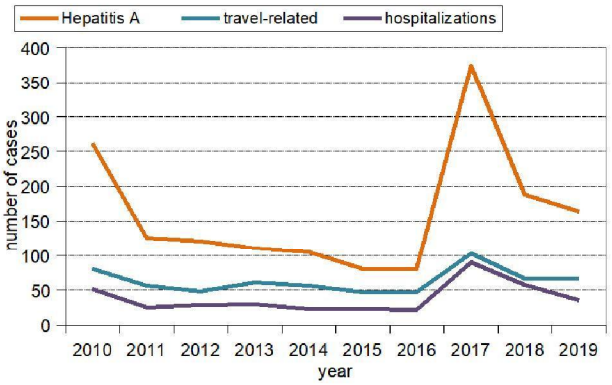

Figure 9.1.1 Number of reported, hospitalised and travel-related cases of hepatitis A, 2010-2019
Source: Osiris

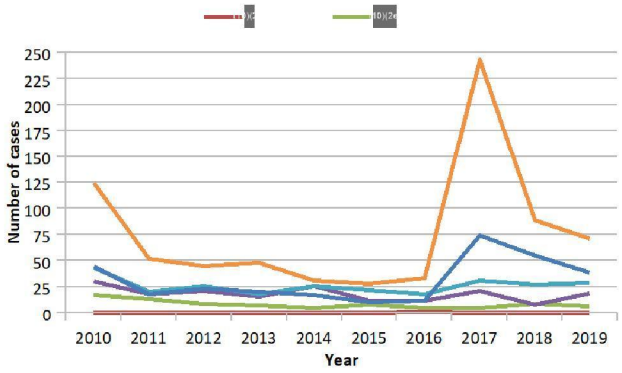

Figure 9.1.2 Age distribution of hepatitis A-cases, 2010-2019
Source: Osiris

9.1.5 *Epidemiology*

A large, international, hepatitis A outbreak occurred in 2017 with in the Netherlands 243 outbreak-related cases. Two-third of these cases were men who have sex with men (MSM) [1]. The outbreak lagged in 2018, both national as international [2]. In 2019, two new strains caused again outbreaks among mainly MSM with seven (five MSM) and 41 cases (22 MSM), respectively.
In 2019, 164 cases of hepatitis A were reported in the Netherlands, corresponding to 0.9 cases per 100,000 population. This is a small decline compared to 2018 (n-188), but it is still higher than in the years 2011-2016 where 80-125 cases were reported (Figure 9.1.1 / Appendix 2). No mortality due to hepatitis A was reported in 2019. The age distribution over the years 2009-2018 is given in Figure 9.1.2. Infections are mainly seen in the 20 to 49 years old. Adults (> 19 years) account for 67% of the cases. In total 35 patients were hospitalised (21%), which is on the low end of percentages hospitalizations seen in the previous years (2010-2018: 20-30%; mean: 24%).

The percentage of travel-related cases was between 28% (2017) and 59% (2015) in previous years (2010-2018; mean: 39%). In 2019, the proportion of travel-related cases was in between with 41% (Figure 9.1.1). Among travel-related cases Morocco (30/67; 45%) was reported most frequently; other countries were reported four times or less. Based on the notifications, 21 epidemiologically linked clusters could be deduced of which 14 clusters at least partly travel related (Morocco: 10 clusters). Ten of these epidemiologically linked clusters were molecularly confirmed. In the other clusters, for none or only one of the cases within the particular cluster a strain was available.

9.1.6 *Pathogen*

Hepatitis A virus (HAV) specific IgM-positive samples can be sent to IDS of the RIVM for typing as part of the molecular surveillance of this virus. In 2019, of 136 of 164 reported cases (83%) samples were submitted

for virus typing. 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 the samples of cases 131 (96%) were positive by PCR and available for sequence analysis. A total of 294 serum and faecal samples of 274 unique persons were tested. HAV RNA was detected in 148 samples (50%) and 129, of reported cases, could be typed which resulted in 58 unique sequences; a total of 90 cases could be assigned to clusters of two or more cases. These concerned 20 molecular clusters varying between two and 41 cases. In 2019, there were no major foodborne hepatitis A clusters in the Netherlands. A single case probably belonged to a cluster in Germany, for which the vehicle was probably strawberries.
The three different strains that circulated in the MSM-outbreak in 2017, were not present in 2019. However, two new strains caused outbreaks among MSM. Early in the year, a IB strain, closely related to strains circulating in the US, caused 7 cases of which 5 among MSM. From the end of March to the end of July, a IA strain caused a total of 41 cases of which 23 were MSM. This strain was also reported in Ireland and Denmark and twice in England.
All clusters were contained by contact tracing and vaccination. At the end of the year a cluster was detected with three cases in 2019, which continued in 2020 with another 14 cases. Transmission occurred within households and a school.
Progress has been made towards whole genome sequence analysis for HAV. The biggest advantage is the increased resolution which makes it possible to examine transmission chains in outbreaks and which also reveals small differences between old and recent strains from the same origin.

9.1.7 *Research*

The international outbreak of hepatitis A in 2016-2018 and the smaller outbreaks in 2019 in the Netherlands show susceptibility to the virus in adults, and especially in MSM. An analysis is ongoing to determine whether vaccination of MSM could be cost-effective.

9.1.8 *International developments*

Bravo et al [3] reviewed the safety and immunogenicity of the Avaxim 80U Pediatric Hepatitis A vaccin. They included nine Sanofi Pasteur sponsored studies. Pooled analyses of these studies showed a consistent >95% of participants with concentrations ≥20 mIU/ml after the first dose and near 100% after the second dose (two cases of vaccin failure have been reported). The geometric mean concentrations (GMCs) after the second dose were around 30% lower among 12-15 year-olds compared to the 12-23 month-olds and 2-11 year-olds. Also three independent studies (included age group(s) within 12 months to 15 years) are described, in which 100% seroprotection was reported after the second dose. Anti-HAV antibody GMCs appear to increase quicker after the first dose when using Avaxim 80U Pediatric compared to other childhood HAV vaccines, which may be relevant when rapid immunization is required.

In Mendoza, Argentina, data of ten years of follow-up (2008-2018) after vaccination with Avaxim 80U Pediatric are completed [4]. Two groups are followed: 436 children with routine HAV vaccination with 1 dose and 108 children with 2 doses. Ten children (group 1: n=9; group 2: n=1) received a booster after having titres below the seroprotective treshold in the first seven years (none happening between seven and ten years of follow-up), and were excluded from analyses. At ten years of follow-up, 190 (group 1) and 51 (group 2) participants remained for analyses. Seroprotection (≥3 mIU/ml by electrochemiluminescence immunoassay (ECLIA)) was 100% in both groups at year 10. GMCs were 78 [95% CI: 69.8-87.6] mIU/ml in group 1 and 352 [271-456] mIU/ml in group 2. Modelling of the available data demonstrated seroprotection of 89% (1 dose) or 85% (2 doses) after 30 years with higher predicted GMCs after 2 doses (37 [13-97] mIU/ml) compared to 1 dose (19 [11-34] mIU/ml).

In South Korea, children aged 12 to 18 months received two doses of Avaxim (n=37), Epaxal (n=34) or Havrix (n=37) [5]. At four to six weeks after the second dose, seropositivity (≥20 mIU/ml) was 100% in all three groups. GMCs increased to 5836.9 [95% CI: 4188.0-8022.8], 1957.3 [1159.0-2908.2], and 2221.3 [1404.8-3410.7] mIU/ml, respectively. The differences in GMCs between Avaxim and the other two vaccines were significant.

Data of 11 years of post-immunization with the inactivated vaccines Healive and Havrix are reported by Wang et al. [6]. Three hunderd Chinese children were assigned to the Healive vaccine and 100 children to the Havrix group (control group), all aged between 1 and 8 years. Both vaccines were given twice, with six months between vaccinations. At the 11-year follow-up visit, 217 and 92 persons were present, respectively. The GMCs were significantly higher in the Healive group compared to the Havrix group at each time point from 1 to 138 months (n=10). At 138 months, the GMCs were 166.2 (Healive) and 117.1 (Havrix) mIU/ml and seroprotection rate was 100% in both groups. Modelling of the available data indicates that Healive will be efficacious for at least 30 years.

In November 2012, HAV vaccination was added to the routine vaccinations in Turkey. Within January 2008 and December 2015, a total of 272 children (<18 years) diagnosed with HAV infection at one of five hospitals in Ankara were enrolled [7]. Most children got infected before the start of the routine vaccination, 72 cases (31.7%) got ill after the introduction. Among the cases, only one child was vaccinated (0.4%), for 27 (9.9%) the immune status was unknown, the other 244 children were unvaccinated (89.7%).

Recruits of the army in South Korea receive a single-dose HAV vaccination since 2013 [8]. The effectiveness of this administration schedule was analysed. The total observation period between 1 January 2013 and 31 December 2016 was 603,550 and 1,020,450 person-years for the vaccinated and unvaccinated group, respectively. A total of 24 confirmed cases of hepatitis A occurred, of which three in the vaccinated group. Vaccine effectiveness was estimated to be 75.9% [95% CI: 19.0-92.8].

In a study of 131 HIV-positive, HAV-negative adults, 77 were vaccinated with HAV/HBV co-vaccine Twinrix (when also HBV-negative; 3 doses) and 54 with an HAV mono-vaccine (2 doses) [9]. A total of 81.5% in the mono-vaccine group and 79.2% in the Twinrix group developed anti-HAV antibodies. Vaccine response depended on absolute CD4 cell count and CD4/CD8 ratio in the mono-vaccine group, and only on age and sex in the Twinrix group. Patients whose titers were checked after more than 5 years were less often seropositive (66.6%; 20/30) than those checked within a year of vaccination (88.9%; 40/45). These results suggest a lower response to hepatitis A vaccination and a possible quicker decline in titers than in immune-responsive adults.

During July 1, 2016–February 7, 2020, US' state health departments publicly reported >31,000 outbreak-associated cases, primarily affecting persons who use drugs and persons experiencing homelessness. More than 18,900 (61%) outbreak-associated patients have reportedly been hospitalized in these outbreaks. Hofmeier et al. estimated the average direct medical costs per hepatitis A–related hospitalization, which can be used to guide investment in outbreak prevention efforts [10]. Overall, the average costs per hepatitis A–related hospitalization in the United States in 2017 were $16,232 (95% CI $15,052–$17,411). Despite longstanding vaccination recommendations for adults at increased risk for hepatitis A virus infection or adverse consequences of infection, self-reported adult hepatitis A vaccination coverage with >2 doses was only 10.9% for persons >19 years of age in 2017. These findings underscore the importance of improving hepatitis A vaccination coverage among at-risk adults.

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*RIVM publication.

9.2 Respiratory Syncytial Virus

A.C. Teirlinck, [redacted]. (10)(2e), W. van der Hoek, P.B. van Kasteren, N.A.T. van der Maas

9.2.3 *Key points*

- A total of 95 RS-viruses (6,4%) were detected in 1493 combined nose swabs and throat swabs of patients with an acute respiratory infection (ARI), collected by sentinel GPs in the 2019/2020 respiratory season, compared with 12% in 2018/2019, 6% in 2017/2018 and 12% in 2016/2017.
- Due to the Covid-19 pandemic, more samples were collected with different age distribution than previous seasons in weeks 10-20, possibly partly explaining the relatively low RSV percentage.

9.2.4 *Tables and figures*

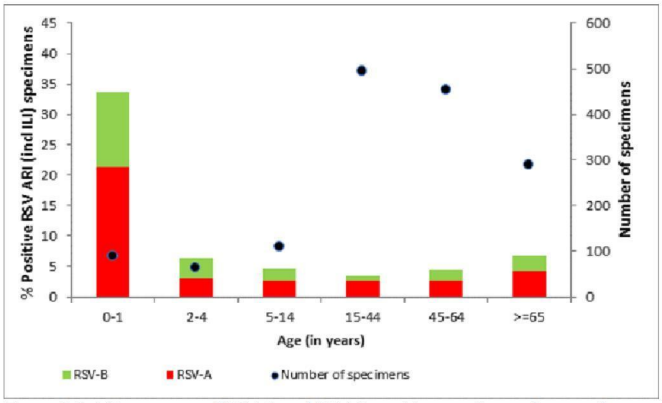

Figure 9.2.1 Percentage of RSV-A and RSV-B positive specimens from patients with acute respiratory infections (ARI), and the number of tested specimens, taken by sentinel general practitioners (GPs) from community patients during the respiratory season of 2019/2020 (week 40 of 2019 - week 20 of 2020), displayed for six age groups. (Source: NIVEL Primary Care Database, RIVM).
Please note that the ARI syndrome also include influenza-like illness (ILI). ILI patients were oversampled because of de setup of the influenza sentinel surveillance.

9.2.5 *Epidemiology and pathogen*

Studies show that RSV is a common cause for respiratory infections in young children [1] and in the elderly [2, 3] causing outbreaks in elderly care facilities (Meijer, Overduin et al. 2013). RSV is subdivided in RSV-A and RSV-B, mainly based on the variation in the attachment protein, the G-protein.

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

In the season 2019/2020, 95 RS-viruses were detected in 1493 nose swabs and throat swabs (6.4%) collected from patients with an acute respiratory infection (ARI) by sentinel GPs. The percentage of positive specimens from the GP sentinel surveillance was lower in this season compared to the previous seasons 2018/2019 (12%) and 2016/2017 (12%) and similar to 2017/2018 (6%). This current season, more samples were collected with different age distribution than previous seasons in weeks 10-20, due to the COVID-19 pandemic, possibly partly explaining the relatively low RSV percentage.
Of the 95 specimens (two patients had a double infection with RSV-A and RSV-B), 61 were RSV-A (64%) and 34 were RSV-B (36%).
The percentage of positive samples was highest in the 0-1 year-olds (34%) and lowest in the 15-44 years-olds (3.4%) (Figure 9.2.1).
See for more information on epidemiology in the Netherlands the annual report 'Surveillance of influenza and other respiratory infections in the Netherlands: winter 2019/2020' that is expected in December 2020.

9.2.6 *Research*

European collaboration on surveillance of RSV and better harmonization in both epidemiological and virological aspects of surveillance is important to strengthen surveillance of RSV at national and European level. RIVM plays an important role in European initiatives on RSV surveillance and works closely together with ECDC and other public health institutes, specifically SSI (Denmark). As a result of this European initiative, an online survey was held in August and September 2017 among EU/EEA countries (n=31) [4]. The questionnaire covered questions on epidemiological and laboratory aspects of RSV surveillance. Eighteen countries reported to have a sentinel surveillance system, 26 countries a non-sentinel surveillance system and three countries to have neither. RSV data collection was mostly done within the context of influenza surveillance. A wide range of diagnostic and characterisation assays was used for the detection of RSV. The prevailing integration of RSV surveillance into the existing influenza sentinel surveillance system may lead to under-reporting of RSV. In the light of a future vaccination programme targeting RSV, the surveillance should be strengthened.

Also, RIVM is partner in the RESCEU project ([http://resc-eu.org/], funded by the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement 116019, receiving support from the European Union's Horizon 2020 research and innovation programme and the European Federation of Pharmaceutical Industries and Associations). This project aims to explore the clinical, economic and social burden from RSV and strengthen European collaboration by the many different disciplines working on RSV. The aim is to create a sound epidemiological and virological baseline, before the introduction of a vaccine, to identify appropriate target groups for vaccination. As part of the RESCEU project, RIVM therefore combines data from several sources, such as hospitals, general practitioners and the national perinatal registry, to get a better insight in the burden of RSV in the Netherlands [5, 6].

Within this project, a high throughput multiplex immunoassay, measuring antibody levels against 4 RSV proteins simultaneously, is

developed [7]. Using this multiplex, the seroprevalence of RSV in a sample of the Dutch population was measured [8]. Results show that maternal IgG concentrations decline up to 10-12 months of age. After the first year of life, approximately 40% of the children lack infection-induced IgA antibodies and may therefore be uninfected. All Dutch children show serological evidence of RSV infection by the age of 3 years. Antibody concentrations reach a plateau by 5-9 years of age that remains constant throughout life. COPD patients have similar levels and avidity of RSV-specific IgG antibodies compared with age-matched healthy controls.

In addition to epidemiological data, a thorough understanding of the immunological mechanisms underlying (protection from) severe RSV disease is essential for advising on the implementation of novel vaccines. We have recently shown that activation of certain immune cells by (maternal) antibodies is decreased in children with severe RSV disease compared to controls [9]. Furthermore, we showed that activation of these cells correlates with the glycosylation status of the RSV-specific antibodies. These findings highlight that the protective efficacy of RSV-specific antibodies may not depend on neutralization alone.

9.2.7 *International developments*

Currently, a phase 2B clinical trial of a subunit RSV vaccine targeting pregnant women is ongoing [10]. The same vaccine will be administered in a phase 3 clinical trial, that will start in the summer of 2020. Several hospitals in the Netherlands will participate in this study. Several other RSV vaccines and monoclonals are in various stages of (clinical) development [https://path.azureedge.net/media/documents/RSV-snapshot-2020_03_26_High_Resolution_PDF.pdf]. Currently, Covid-19 vaccines using several vaccine platforms are developed. The knowhow that is gained through these developments can be used in the development of RSV vaccines.

9.2.8 *Literature*

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*RIVM publication.

9.3 Rotavirus

M. Middeldorp, I.K. Veldhuijzen, H. Vennema, A.W.M. Suijkerbuijk, M. Hooiveld, R. Pijnacker, P. Bruijning-Verhagen, H.E. de Melker.

9.3.3 *Key points*

- The number of rotavirus detections in 2019 was slightly lower than in 2018. In 2020, until May, fewer rotavirus detections have been reported compared to the same period in 2019. A marked reduction in the number of rotavirus detections have been observed per March 2020.
- G9P8 and G3P8 were the most prevalent genotypes in 2019.
- The Ministry of Health, Welfare and Sport has decided to delay the implementation of rotavirus vaccination in the National Immunization Program. In the RIVAR study lower vaccine-effectiveness estimates were unexpectedly found for high risk infants. The Ministry requested a new advice from the Health Council.

9.3.4 *Tables and figures*

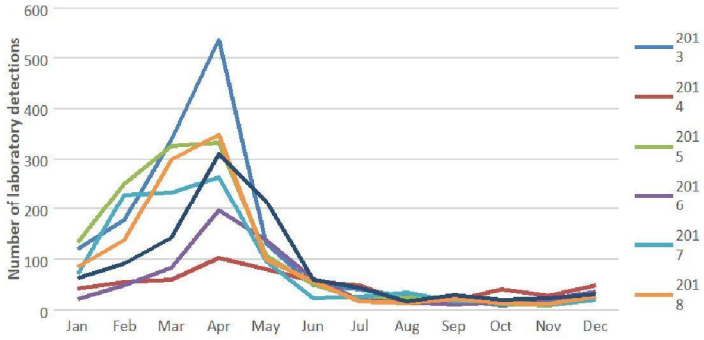

Figure 9.3.1 Number of reported laboratory rotavirus detections per month in the Netherlands, 2013-2019

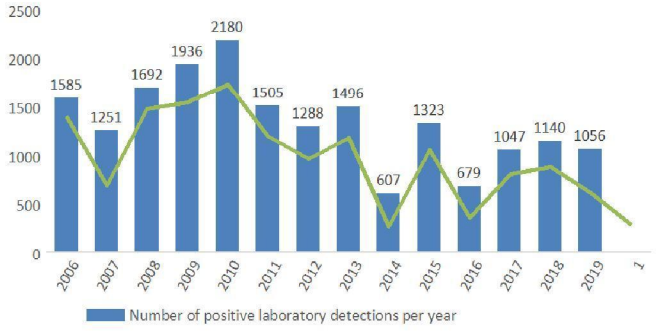

Figure 9.3.2 Number of reported laboratory rotavirus detections per year and between January and May in the Netherlands, 2006-2020

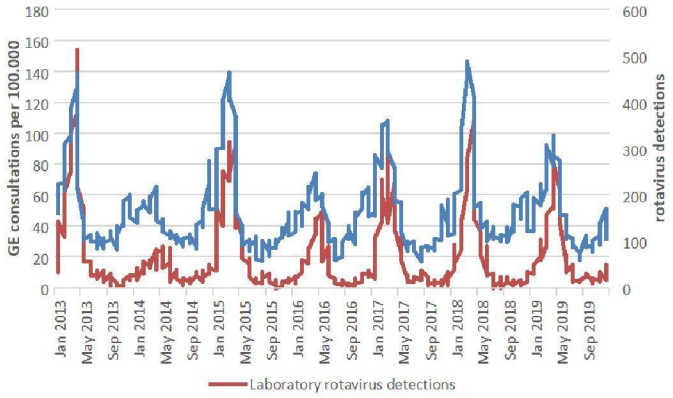

Figure 9.3.3 Overall number of rotavirus laboratory detections and general practice all-cause gastroenteritis consultation in children under 5 years old per week, the Netherlands, 2013-2019

Table 9.3.1 Number of rotavirus samples typed per year and identified genotypes, the Netherlands, 2013-2019

Type	2013	2014	2015	2016	2017	2018	2019	Total
G12P8	1	6	2	0	1	2	1	13
G1P8	**83**	20	25	9	23	7	12	179
G2P4	41	29	34	12	12	6	13	147
G3P8	51	7	14	23	**38**	56	**40**	229
G4P8	35	12	**137**	3	23	3	0	213
G9P8	23	**49**	32	**59**	20	**60**	38	281
G9P4	1	0	1	0	8	29	24	63
Other	52	16	27	12	42	16	17	182
Total	287	139	272	118	167	179	145	1307

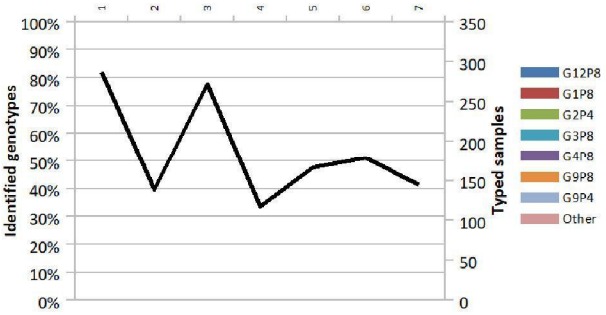

Figure 9.3.4 Absolute number of rotavirus samples genotyped per year and the proportions of identified genotypes, the Netherlands, 2013-2019

9.3.5 *Epidemiology*

Rotavirus infections are not notifiable in the Netherlands, and therefore data sources other than those for notifiable diseases were used. Namely, the weekly virology report and the Nivel Primary Care Database.

9.3.5.1 Weekly virology report

In 2019, 1,056 rotavirus cases were notified, slightly less than in 2018 (n=1,140) (Figure 9.3.2). Most rotavirus laboratory detections were reported between February and May (72%), with a peak in the last week of April (81 rotavirus laboratory detections) (Figure 9.3.1). Data from 2020 up to May show almost half of the rotavirus cases compared to the same period in 2019 (2019 n=610; 2020 n=284) (Figure 9.3.2). The difference in number of rotavirus detections is mainly due to a sharp decrease in April 2020 (2020 n=13; 2019 n= 311). This decline in Rotavirus detections is likely mainly due to the preventative measures taking during the COVID-19 pandemic such as the closure of schools and increased hand washing [1].

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 2019 contradict this hypothesis (Figure 9.3.2).

9.3.5.2 Nivel

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

In 2019, 8,102 all-cause GE consultations were reported per 100,000 children younger than five years of age (on average 164 per 100,000 per week) (Figure 9.3.3). This were less consultations compared to 2018 (n=9,838 per 100,000). Consultations in 2019 were more frequent between January and mid-July with a peak in mid-April (330 per 100,000 children per week). In this period of the year, 5580

consultations per 100,000 children were registered, which is less than the number of consultations registered in the same period in 2018 (n=6,430 per 100,000).

9.3.6 *Pathogen*

The IDS/RIVM receives faecal samples throughout the year from the Working Group Clinical Virology laboratories for rotavirus genotyping. The results are given per calendar year and are shown in Table 9.3.1. and Figure 9.3.4.

In 2019, 145 of 166 the received samples (87%) could be typed (Table 9.3.1). Almost half of the typed samples (62/145) were identified as rotavirus G9, which comprises the genotypes G9P8 and G9P4. The most prevalent genotypes were G9P8 and G3P8, which accounted for, respectively, 26% (38/145) and 28% (40/145) of the typed samples (Figure 9.3.4).

Since the COVID-19 control measures were implemented around mid-March 2020, only 1 sample have been received up to May. From January to mid-March, 36 samples have been received, of which 5 were not typable, and about half of the samples were identified as rotavirus G9.

9.3.7 *Research*

9.3.7.1 RIVAR study

Between May 2016 and November 2017 the RIVAR study (Risk-Group Infant Vaccination Against Rotavirus) offered 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 participating Dutch hospitals. This project was a pilot study on the feasibility and effectiveness of rotavirus vaccination in high-risk infants. Of the infants eligible for rotavirus vaccination, 49% (726/1482) were vaccinated. Survival probabilities for severe rotavirus AGE for vaccinated and unvaccinated infants between 2 and 18 months of age did not differ between the groups [3]. Vaccine effectiveness for severe rotavirus AGE in the high-risk infants was lower than expected, namely 30% (95% confidence interval, -40%–65%) compared with previously reported 68% to 98% in healthy infants [4]. The RIVAR study showed no reduction in all-cause severe AGE between vaccinated and unvaccinated high-risk infants.

9.3.8 *Cost-effectiveness*

Kotsopoulis et al. assessed the financial consequences of rotavirus vaccination for families, employers and authorities in the Netherlands [5]. A Social Accounting Matrix (SAM) framework has been developed reflecting the distribution of income and spending at equilibrium affected by rotavirus disease among all those concerned for 1 year. The total financial cost difference at equilibrium between presence and absence of rotavirus vaccination was +€26.758 million over one year as a net economic surplus. The payment of vaccination (€19.194 million) by the government was offset by the increase in tax revenue (€14.561 million) and by the lower spending in treatment care (€7.998 million). The manufacturers pay corporate taxes on the profitability of their goods sold. Moreover, vaccination prevents parents being absent from work which is associated with increased productivity, higher wages, more

spending, increased tax revenue, and reduced healthcare costs. This study was funded by GSK.

9.3.9 *(Inter)national developments*

In April 2020, the Ministry of Health, Welfare and Sport decided to delay the implementation of the rotavirus vaccination in the National Immunization Program due the unexpected lower estimates of vaccine-effectiveness found in the RIVAR study for high risk infants [6]. The Ministry will again submit a new request for advice to the Health Council on rotavirus vaccination.

As of April 2020, worldwide, 107 countries have introduced rotavirus vaccination in their national immunisation programmes. In addition, four countries have either phased or sub-national introductions. Of the ten countries with the highest numbers of rotavirus-related deaths, seven countries introduced rotavirus vaccination (Afghanistan, Angola, Ethiopia, India, Kenya, Niger, and Pakistan) [7]. Four World Health Organization (WHO) prequalified rotavirus vaccines are available, namely ROTASILL, ROTAVAC, Rotarix, and RotaTeq [8]. Only Rotarix and RotaTeq are licensed for use in Europe [10].

A systematic literature review on the global impact of rotavirus vaccination on diarrhoea hospitalizations and deaths among children <5 years old analysed published data from 2006-2019 with at least 12 months of data before and after rotavirus vaccine introduction [10]. The review shows a median reduction in rotavirus hospitalizations between 46-74%, AGE hospitalisations between 23-47%, and AGE mortality between 28-46%. The reductions were larger in countries with low child mortality, among younger age groups, and in countries with higher rotavirus vaccination coverage.

9.3.10 *Literature*

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9.4 Varicella zoster virus (VZV) infection

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9.4.3 *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 2018 GPs recorded about 45,000 varicella and 93,000 herpes zoster episodes (260 and 540 episodes per 100,000 population respectively).
- In 2020, the Health Council of the Netherlands issued a positive recommendation to add vaccination against varicella in the NIP in the Caribbean Netherlands and not in the European Netherlands. The council also recommends that residents of these islands who have not yet had an infection be offered a one-off vaccination against VZV.
- In July 2020, the revised Dutch guideline 'Varicella' has been published. It includes revised opinions on post-exposure prophylaxis (PEP) and a new module on varicella treatment.

9.4.4 *Tables and figures*

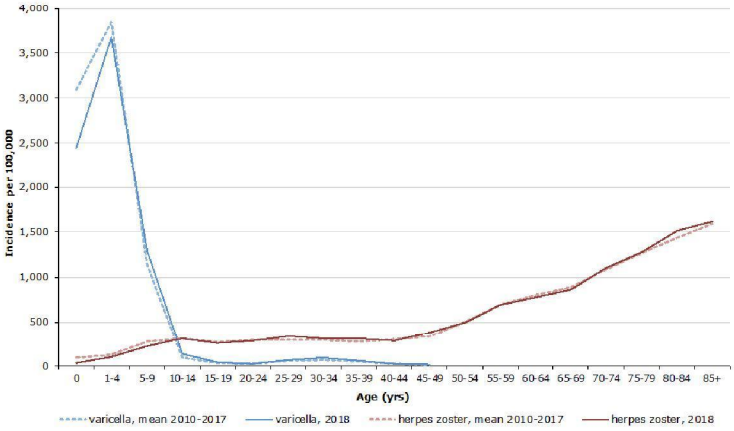

Figure 9.5.1 Estimated incidence per 100,000 population of episodes of varicella (ICPC-code A72) and herpes zoster (ICPC-code S70) in 2018 versus mean 2010–2017 by age group [1]

Note: Varicella cases in people over 49 years of age are only sporadically reported by GPs and therefore not included.

Source: NIVEL

Table 9.5.1 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 (2008–2011) and new method (2010–2018) (rounded off to closest ten)

Syndrome	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Varicella*	(160)	(110)	(180)								
Varicella**	290	180	210	230							
Varicella***			310	270	250	280	270	250	240	280	260
Herpes zoster**	340	360	360	360							
Herpes zoster***			480	490	510	510	530	530	530	530	540

* 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 9.5.2 Incidence per 100,000 population of hospitalisations due to main diagnosis of varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02), 2008–2018 [4]

Syndrome	2008	2009	2010	2011	2012	2013	2014	2015*	2016*	2017*	2018*
Varicella	1.7	1.5	1.9	1.7	1.5	1.7	1.9	1.9	2.1	2.0	1.8
Herpes zoster	2.0	2.4	2.1	2.2	2.1	2.1	2.7	3.0	2.9	2.9	3.2

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 9.5.3 Absolute number of deaths with varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02) as primary cause of death, 2008–2019 [5]

Syndrome	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019*
Varicella	0	1	2	1	2	1	2	2	4	3	2	3
Herpes zoster	14	20	25	20	21	21	26	33	27	33	36	32

* Preliminary data
Source: CBS

9.4.5 *Epidemiology*

The VZV epidemiology in the Netherlands is comparable to that in previous years (Tables 9.5.1, 9.5.2 and 9.5.3). In 2018, general practitioners (GP) recorded about 45,000 varicella and 93,000 herpes zoster (HZ) episodes (260 and 540 episodes per 100,000 population respectively). The incidence of GP consultations due to varicella episodes per 100,000 population is highest in children aged under five, whereas the incidence of GP consultations due to HZ episodes is highest in those aged over 50 (Figure 9.5.1). According to a new, more precise method for estimating morbidity rates used by NIVEL from 2012 onwards [6],

the incidence of HZ is higher than it was according to the old method (Table 9.5.1). 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 [7]. 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 2019, we would expect 4.3 deaths (range 1.7–6.6 instead of the 32 deaths reported preliminary in 2019 (Table 9.5.3).

9.4.6 *Research*

Recently, results of the sero-epidemiological study to obtain insight into VZV susceptibility and its determinants in island populations of the Caribbean Netherlands have been published. Overall VZV seroprevalence in the Caribbean Netherlands was 78%, being lowest on St. Eustatius (73%) and highest on Bonaire and Saba (79%) [8]. This was considerably lower than in the Netherlands (96% based on preliminary results of the Pienter 3 study (2016/2017) and 95% based on the Pienter 2 study (2006/2007) [9]).

Because of the lower VZV seroprevalence in the Caribbean Netherlands, the disease burden of varicella is higher than in the European Netherlands. Therefore, in 2020, the Health Council of the Netherlands issued a positive recommendation to add vaccination against varicella to the NIP (by replacing MMR with MMRV vaccine) in the Caribbean Netherlands and not in the European Netherlands. The council also recommends that residents of these islands who have not yet had an infection be offered a one-off vaccination with a monovalent varicella vaccine. For residents over 50 years old, the council recommends using a herpes zoster vaccine.To support the advice of the council, the RIVM has gathered background information on vaccination against varicella. This overview provides, among other things, information on the number of people in the Netherlands who fall ill each year, the efficacy and safety of vaccines, and the public's opinion on varicella vaccination [10].

In July 2020, the revised Dutch guideline 'Varicella' has been publised (https://richtlijnendatabase.nl/nieuws/richtlijn_varicella_herzien.html). This is a guideline for all professions involved in the care of varicella patients (medical specialists, GPs, nurses, midwives or other health care providers) and patients who are dealing with persons with varicella or who have been exposed to varicella. In particular, the opinions on post-exposure prophylaxis (PEP) have been revised in the guideline, and a new module on varicella treatment has been included [11].

9.4.7 *International developments*

9.4.7.1 Varicella

A study in England, showed an increasing trend over time between 2004 and 2017 in the incidence of varicella hospitalisation and the proportion of admissions with complicated varicella. The reason is unclear but it may be related to improvements in coding over time or a shift in health care utilisation from primary to secondary care [12]. In Germany, where universal varicella vaccination was introduced in 2004, the incidence of varicella-related complications based on hospital data decreased by 77% from 2005 to 2011. The strongest reductions were seen in children <5 years of age (90%) and for varicella-related complications of the

respiratory tract (upper 97%; lower 90%) [13]. In Lu'an, China, with a one-dose voluntary vaccination programme (payment by parents), an increase in reported varicella cases was seen in all age groups including an age shift from 5–9 years to 10–14 years at a moderate overall vaccination coverage of 71.7% (95%CI: 68.5–73.4%) [14]. A population-based study in the United States showed that the HZ incidence rate among children who were vaccinated against varicella (38 per 100,000 person-years) was 78% lower than that among unvaccinated children (170 per 100,000 person-years). Furthermore, the overall incidence of paediatric HZ declined by 72% from 2003 through 2014 [15]. A small study among women of childbearing age showed that natural varicella infection induced higher VZV-specific T cell immune responses than varicella vaccination. Therefore, vaccinated women may be at increased risk of breakthrough varicella but larger studies are needed to confirm this [16].

9.4.7.2 Herpes zoster

A Japanese study using a VZV skin test to measure cell-mediated immunity (CMI) and a serological essay to measure VZV-specific antibodies confirmed that CMI plays an important role in preventing development of HZ, whereas humoral immunity does not [17]. A small study measuring saliva VZV DNA persistence suggested that an initial low VZV CMI response and persistence of VZV DNA in saliva may be associated with the development of postherpetic neuralgia (PHN), even after adjustment for age [18]. Whereas previous studies have varying conclusions on whether HZ is seasonal, results of a large insurance claims database study suggested that the incidence of HZ exhibits an annual trend with a peak in the summer [19]. Forbes et al. conducted a self-controlled case series study using UK electronic healthcare data to explore the exogenous boosting hypothesis. Their study suggested that exogenous boosting provides some protection from the risk of HZ, but not complete immunity. In the two years after household exposure to a child with varicella, adults were 33% less likely to develop HZ compared with baseline time. In the 10–20 years after exposure this was 27% [20]. This may have consequences for cost-effectiveness analyses of childhood varicella vaccination that include effects on the occurrence of HZ.

In Australia, the cumulative uptake in the target population two years after implementation of a national HZ programme with the attenuated zoster vaccine live (ZVL, Zostavax®) for 70–79 years old was estimated at 47% [21]. In the two years since programme launch, HZ antiviral prescription rates decreased in this age group, by an average of 13.6% (95%CI: 1.5–24.2%) per year [22]. Based on data on GP consultations and hospitalisations for HZ and PHN, Andrews et al. showed evidence of sustained population impact of the HZ vaccination programme (with ZVL) 5 years following its implementation in England. Vaccine efficacy was estimated to be approximately 50% to 60% which suggests that the protection from the vaccine does not wane as rapidly in clinical practice compared with the trial settings [23]. The uptake of ZVL in the United States was estimated at 5.7% in adults aged 50–59 years (approved for use but not recommended) and 34.9% in adults aged ≥60 years (recommended in 2006) in 2017 [24]. In a retrospective population-based study conducted with health care registry data from Stockholm

County (Sweden), the overall vaccine effectiveness of ZVL was 34% (hazard ratio (HR) = 0.66; 95%CI: 0.55–0.78) in vaccinated persons. The VE stratified by age was: 50–60 years of age 47% (HR = 0.53; 95%CI: 0.21–1.30), 61–75 years of age 43% (HR = 0.57; 95%CI: 0.44–0.73), and in persons above 75 years 7% (HR = 0.93; 95%CI: 0.68–1.26) [25]. Klein et al. found an overall vaccine effectiveness of ZVL of 64.8% (95%CI: 61.3–68.0%) against PHN. The effectiveness was 82.8% (95%CI: 77.6–86.7%) during the first year after vaccination and waned to 48.7% (95%CI: 30.2–62.3%) during the eighth year after vaccination [26]. Weinberg et al. showed that the lower vaccine immunogenicity of ZVL in older adults is influenced by baseline regulatory T cells (Treg and Tcheck) and VZV-specific T cell immunity. They suggested that immune modulators that block regulatory T cell activity may increase vaccine responses in older adults [27].

Post-hoc analyses of two efficacy studies (ZOE-50 and ZOE-70) of the adjuvanted recombinant zoster vaccine (RZV, Shingrix®) suggested that the number and type of medical conditions at enrollment did not impact the efficacy and safety of RZV [28]. Furthermore, RZV appeared to be effective irrespective of sex, region, or geographic ancestry/ethnicity [29]. Dagnew et al. showed that 2 doses of RZV induced strong humoral and polyfunctional CMI responses in adults ≥65 years, irrespective of previous ZVL vaccination [30]. Hastie et al. showed that immune responses to two initial RZV doses in older adults persisted through 10 years after vaccination and are predicted to persist ≥20 years after vaccination. One additional RZV dose after the initial 2-dose course elicited strong immune responses with no further increase after a second additional dose [31].

A study in the United Kingdom showed that being proactively offered the vaccine by a GP or nurse, perceiving to be at risk of developing HZ and perceived self-efficacy were associated with HZ vaccine uptake [32]. In the United States, where HZ vaccination is recommended since 2008, three surveys among primary care physicians were conducted in 2005, 2008 and 2016. Ten years after licensure of ZVL, physicians were more likely to respond that they perceived HZ as a serious disease and more strongly recommended ZVL. Furthermore, they were less likely to report several major barriers to HZ vaccination [33].

9.4.7.3 Cost-effectiveness

McGirr et al evaluated the cost effectiveness of RZV compared to no vaccination and to ZVL in Canadians aged 60 years and older [34]. Compared with no vaccination the incremental cost-effectiveness ratio (ICER) of RZV was $28,360 (Canadian dollars) per quality-adjusted life-year (QALY) in persons aged ≥60 years, avoiding 554,504 HZ and 166,196 PHN cases. Compared with ZVL, RZV accrued more QALYs through the remaining lifetime and an increase in costs of approximately $50 million resulting in an average ICER of $2396. This analysis suggested that RZV would be cost effective in the Canadian population compared with no vaccination and vaccination with ZVL at a willingness-to-pay threshold of $50,000. This study was funded by GSK. These results are in line with another, unsponsored, study performed in Canada in which the effectiveness and cost-effectiveness of these two vaccines were compared [35]. The number needed to vaccinate (NNV)

was higher for ZVL than for RZV. For example, in persons 65 years old, for HZ, median NNV was 21 (90% uncertainty interval [UI]: 13–31) versus 8 (90%UI: 6–18), and for PHN, NNV was 64 (90%UI: 33–93) versus 31 (90%UI: 23–73). The authors conclude that RZV is likely cost-effective in Canada for adults 60 years or older, and is likely more cost-effective than ZVL.
Carpenter et al. evaluated the cost-effectiveness of these two vaccinations for the United States [36]. For individuals vaccinated at age 50 years, the ICER for ZVL versus no vaccination was $118 535 per QALY at age 60 years, the ICER dropped to $42 712/QALY. The RZV was more expensive but had better ICERs than ZVL. At age 50, the ICER was $91 156/QALY, and it dropped to $19 300/QALY at age 60. Vaccination with RZV was more cost-effective than ZVL in all age groups studied. Following US threshold for cost-effectiveness, vaccination with RZV at age 50 years appears cost-effective.
In a Japanese cost-effectiveness analysis, the RZV proved to be more effective but also more costly [37]. Therefore, the optimal strategy in Japan depends on the willingness-to-pay threshold.

9.4.8 *Literature*

9.4.8.1 References

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* RIVM publication

9.1.3.2 Other recent RIVM publications

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10. Vaccines in development for other potential future NIP target diseases

N.Y. Rots

An update of information with regard to vaccines in development, for infectious diseases, that have reached the clinical testing phase and are relevant for the Netherlands is given in the table below. Vaccine development takes 10-20 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.
This year the Corona virus SARS-CoV-2 vaccines in development have been added in a separate table. More than 160 vaccines are being developed. Also for these COVID-19 vaccines only the vaccines that are currently (July 2020) being tested in humans have been included in the overview.

10.1 Bacteria

Pathogen	Vaccine	Status, clinical phase
Chlamydia	Adjuvanted chlamydia vaccine CTH522 (SSI/imperial college Londen)	I completed, Safe humoral and cellular immune response
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
	Recombinant protein adjuvant (GSK)	I
Helicobacter pylori	HP3 (Chiron/Novartis)	I/II, 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)/**Pfizer** since 2020	II (fast track FDA)
Meningococcal ABCWY	MenABCWY recombinant conjugated Novartis/GSK,	II adolescents booster dose study completed
		I

	Pfizer	
Moraxella catarrhalis, non-typeable Haemophilus influenza COPD	Recombinant COPD reduction with adjuvant (GSK)	II
Shigella	-Live attenuated single-strain, -Inactivated trivalent whole cell,	I completed II
	-Chemical glycoconjugate -Rrecombinant glycoconjugate (biconjugate) - Conjugate outer membrane (Novartis/GSK)	I III II
Staphylococcus aureus	Conjugate (SA4Ag, 4 antigen), fast track FDA (Pfizer)	II Previous phase I-III with different single antigen vaccine candidates all failed, safety concerns and low efficacy
	Protein	I
Streptococcus group A & B	-Group A: N-terminal M protein-based multivalent vaccines (26-valent and 30-valent)	II
	Conserved M protein vaccines (the J8 vaccine and the StreptInCor vaccine)	I
	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)	II maternal
	Recombinant fusion antigen Minervax APS	I
Tuberculosis (all forms all ages)	-Live attenuated vaccine BCG -2, 3 or 4 antigen adjuvanted fusion protein (GSK/Areas, Areas)	On market but low efficacy 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

10.2 SARS-CoV-2 vaccines

Vaccine type	Company	Status
Inactivated whole virus	Wuhan Institute/Sinopharma (China) Beijing institute/Sinopharma (China) Sinovac (China) Institute Medical Biology (China)	 II III I/II
Live attenuated virus		Pre-clinical
Non-replicating Viral vector	University Oxford/AstraZeneca CanSino Beijing Institute Biotech (10)(2e) Pharmaceutical	III III, used in military I/II start 22 July 2020
Protein (sub-unit)	Novavax Clover Biopharm (China) University Queensland (Australie)	I/II I/II I/II
RNA	Moderna (LNP encapsulated mRNA) BioNTech/Fosun/Pfizer (LNP mRNA) Imperial College London Curevac (Duitsland)	III start July 2020 I/II, III summer 2020 I/II I/II
DNA	Inovio/IVI (DNA plasmid electroporation) Cadila Healthcare Limited Genexine consortium Osaka University/Takara bio (with adjuvant)	I/II I/II I/II I

10.3 Viruses

Pathogen	Vaccine	status
Chikungunya	Live recombinant Measles Virus based Virus-like particle (NIAID) Live attenuated (Valneva)	II, Immunogenic and safe in adults I FDA fast track
Cytomegalo (CMV)	-Glycoprotein B bivalent -DNA (Astellas/ Vical) -Replication defective V160 (MSD)	I and III III failed CMV+ stem cell transplant patients II

	-Stem cell transplant patients (Merck)	Approved US 2017
Dengue	-Live recombinant (tetravalent) (Butantan/NIAID) -Live-attenuated (tetravalent) TDV (Takeda) -Inactivated (tetravalent)V180(Merck) -Recombinant subunit (tetravalent) (GSK) -Monovalent subunit DNA	III III I I/II Dengvaxia Sanofi registration approved for 9-45 years of age
Ebola	-rVSVΔG--ZEBOV--GP V920 (Merck/ NewLink Genetics) -CAd3-EBOZ (GSK/NIH/NIAID) -Ad26-EBOV and MVA-EBOV (Johnson & Johnson/Janssen vaccines and Bavarian Nordic) -Recombinant nanoparticle based (Novavax) -Recombinant viral vector (GSK) -VRC-EBOADC069-00-VP (Okairos, NIAID)	III, approved for compassionate use III I III II I
Epstein–Barr	Recombinant gp350 Glycoprotein subunit Live attenuated vaccines	II 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) Inactivated V212 (Merck)	Approved US and EU III, on hold
HIV	Recombinant protein (GSK) Viral vector Prime/boost (Sanofi) Ad26 Mos HIV vaccine ((10)(2e) vaccines) DNA (GeoVax)	II II III II completed
Hookworm	iBio	I
Noro	Virus-like particles (bi-valent) (Takeda) Oral tablet vaccine (Vaxart)	II I

MERS-CoV	MVA-MERS-S DNA (GeneOne Life Scinence/Inovio)	II
Parainfluenza type I	Live attenuated	I-II
Pneumococcocus	(killed) whole cell vaccine Protein-based vaccines (GSK, Sanofi)	II I, II
Respiratory syncytial (RSV) (17 in clinical development)	Live attenuated (Sanofi/NIH) Live attenuated (intravacc) Inactivated whole cell Nanoparticle based (Novavax) Subunit, F-protein (GSK) Subunit, F-protein (NIH/NIAID/VRC) Subunit, F-protein (Pfizer) Subunit, F-protein ((10)(2e)) Subunit, F-protein (Merck) Gene-based vector MVA (Bavarian Nordic Gene-based vector AV ((10)(2e)) Gene-based vector AV (Vaxart) Gene-based vector AV (GSK)	I (paediatric) I (paediatric) 0 III (maternal data 2021) FDA fast track, II (elderly, failed), II maternal stopped I (paediatric) II maternal I (maternal, elderly) II elderly, maternal I (elderly) II II (elderly) II (elderly, paediatric) I (paediatric) II (paediatric) I/II (maternal, elderly)
Typhoid	TT-Conjugate (Bharat Biotech)	III published
West Nile	Inactivated (NIAID) Live attenuated Recombinant subunit (NIAID Hawai Biotech)	I completed I completed
Zika	DNA (GeneOne Life Scinence/Inovio, NIAID) RNA Live attenuated Whole inactivated (Sanofi, Takeda, NIAID)	II II II (Sanofi did not start phase III limited funding Barda)

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

11. List of abbreviations

4CMenB	multicomponent meningococcal B vaccine
2vHPV	bivalent human papillomavirus vaccine
9vHPV	nonavalent HPV-vaccine
AAPC	average annual percentage change
ACIP	Advisory Committee on Immunisation Practices
AE	adverse events
AEFI	adverse events following immunisation
AGE	acute gastroenteritis
AGW	anogenital warts
aP	acellular pertussis
ARI	acute respiratory infections
ASC-US	atypical squamous cells of undetermined significance
BCG	Bacillus Calmette-Guérin
bOPV	bivalent oral polio vaccine
CBS	Statistics Netherlands
Cc	clonal complex
CDC	Centres for Disease Control and Prevention
cgMLST	core genome Multi Locus Sequence Typing
CI	confidence interval
CIb	Centre for Infectious Disease Control
CIN	cervical intraepithelial neoplasia
CMI	cell-mediated immunity
CMV	Cytomegalovirus
CN	Caribbean Netherlands
COPD	chronic obstructive pulmonary disease
CRM	CRM conjugate
CSF	cerebrospinal fluid
DALY	Disability Adjusted Life Years
DHD	Dutch Hospital data
DNA	desoxyribonucleic acid
DTaP	combination of diphtheria, tetanus and acellular pertussis vaccines
DTaP-IPV	combination of diphtheria, tetanus, acellular pertussis and inactivated polio vaccines
DTP	combination of diphtheria, tetanus and pertussis vaccines
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
Fim3	serotype 3 fimbriae
FU	Follow-up
GAPIII	the WHO global action plan to minimise poliovirus facility-associated risk
GBD	Global Burden of Disease
GE	gastroenteritis

GMC	geometric mean concentrations
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
(H)SIL	high-grade squamous intraepithelial lesions
HSV	herpes simplex virus
HZ	herpes zoster
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
ICPC	International Classification of Primary Care
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
LMICs	low-income and lower-middle-income countries
LMR	National Medical Registration
lrHPV	low-risk human papillomavirus
MenACWY-TT	tetravalent meningococcal tetanus toxoid conjugate vaccine
MenB	Meningococcal serogroup B
MenC	Meningococcal serogroup C
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
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*
NTM	neurotrimin
OPV	oral polio vaccine
OR	odds ratio
PASSYON	Papillomavirus Surveillance among STI clinic Youngsters
PCA	principal component analysis
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
PHN	postherpetic neuralgia
Pienter	assessing immunisation effect to evaluate the NIP
PPV	pneumococcal polysaccharide vaccine
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
rBSA	rabbit Serum Bactericidal Assay
RIVM	National Institute for Public Health and the Environment, the Netherlands
RSV	respiratory syncytial virus
RV	rotavirus
RZV	recombinant zoster vaccine (Shingrix®)
SAGE	strategic advisory group of experts
SHC	sexual health centres
ST	Sequence Type
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

VSCC	vulvar squamous cell carcinoma
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
ZVL	zoster vaccine live (Zostavax®)

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. Data for 2018 is not available yet.

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

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

2014	82	18	99	1

*These numbers are an approximation of the exact percentage
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.
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 since last year. For each birth cohort, the vaccination coverage as reported in the national vaccination coverage report 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.
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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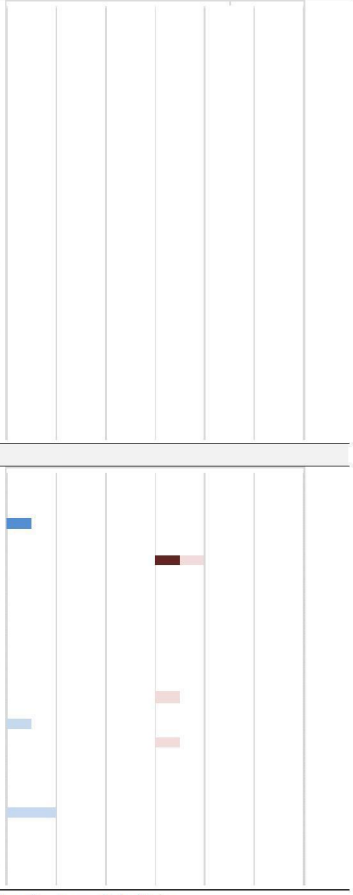
* RIVM publication

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
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**	
2019*	0	0	0	0	0	0	**0**	
*Hospitalisations ** (source: Prisma nt/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.

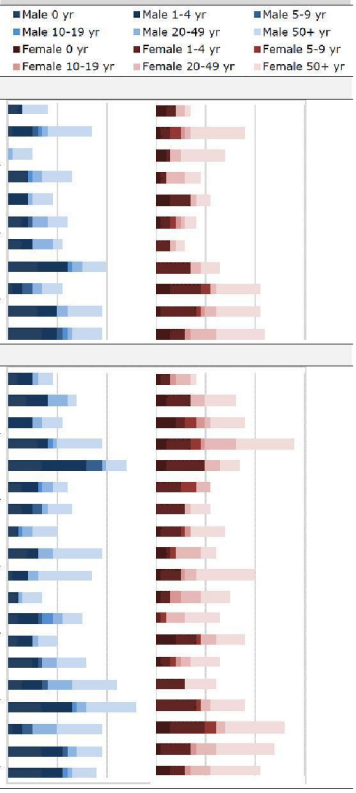
**Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.
^ Data corrected for non-participating hospitals and rounded off to closest five.

Diphtheria								ICD9: 032 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
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**	
2019	0	0	0	0	1	0	**1**	
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**	
2019								

*Number of diphtheria isolates.

Haemophilus influenzae

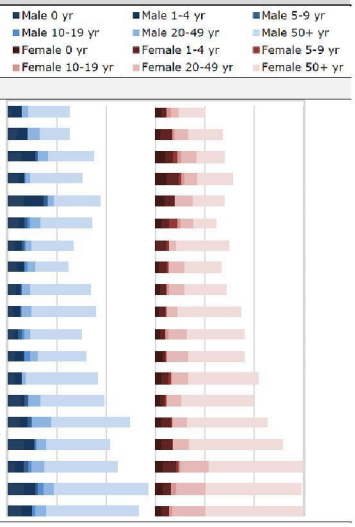
Year	Age (years)						Total
	<1	1-4	5-9	10-19	20-49	50+	
Notifications (serotype b; source: Osiris)*							
2009	4	3	0	0	2	6	**15**
2010	2	6	3	2	2	20	**35**
2011	2	1	0	0	3	13	**19**
2012	5	1	0	1	6	9	**22**
2013	3	8	0	0	2	7	**20**
2014	4	3	2	1	4	6	**20**
2015	3	5	0	0	5	4	**17**
2016	6	13	0	1	4	9	**33**
2017	4	8	4	0	3	13	**32**
2018	7	11	1	1	4	16	**40**
2019	10	6	1	2	6	16	**41**
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**
2019	10	7	0	2	5	15	**39**



*Notifiable since 2009

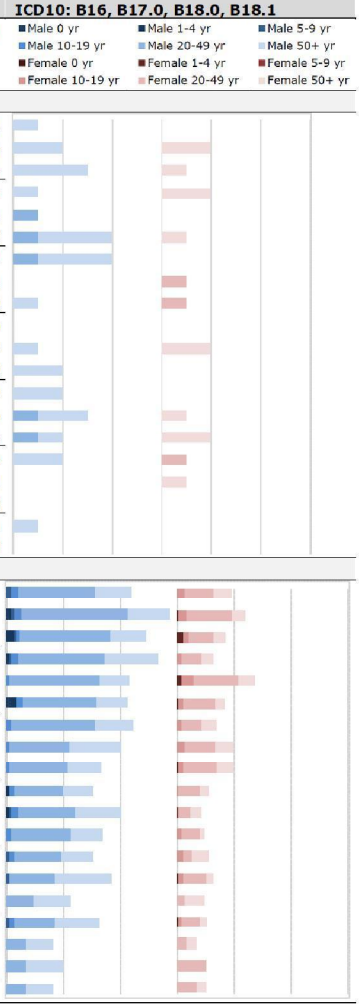
Haemophilus influenzae

Year	Age (years)						Total
	<1	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**
2019	17	15	0	4	36	155	**227**



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

Year	Age (years)						Total
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]+	
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**
2019*	0	0	0	0	0	0	**0**
*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	25	25	**50**
2017^	0	0	0	0	20	20	**40**



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

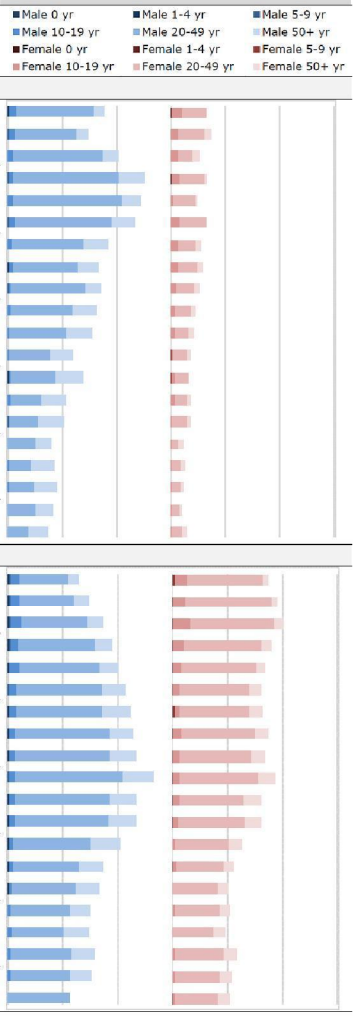
**Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

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

**Age is unknown for 18 patients.

Hepatitis B

Year	Age (years)						Total
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	[illegible]	[illegible]	[illegible]	[illegible]	**[illegible]**
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**
2019	0	0	0	2	58	44	**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	758	253	**1,051**
2019	0	4	4	33	769	291	**1,101**



Hepatitis B

Year	Age (years)	Total	All ages
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		684	
2014		722	
2015		1,174	
2016		754	
2017		981	
2018		933	
2019		763	

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
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**	
2019*	0	0	0	0	26	171	**216**	
Registrations (cervical cancer; source NKR)								
2000	0	0	0					
2001	0	0	0					
2002	0	0	0					
2003	0	0	0					
2004	0	0	0	1	375	327	**703**	
2005	0	0	0					
2006	0	0	0					
2007	0	0	0					
2008	0	0	0					
2009	0	0	0					
2010	0	0	0					
2011	0	0	0					
2012	0	0	0	1	406	328	**735**	
2013	0	0	0					
2014	0	0	0					
2015	0	0	0					
2016	0	0	0					
2017	0	0	0	1	433	339	**773**	
2018	0	0	0					
2019**	0	0	1					

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

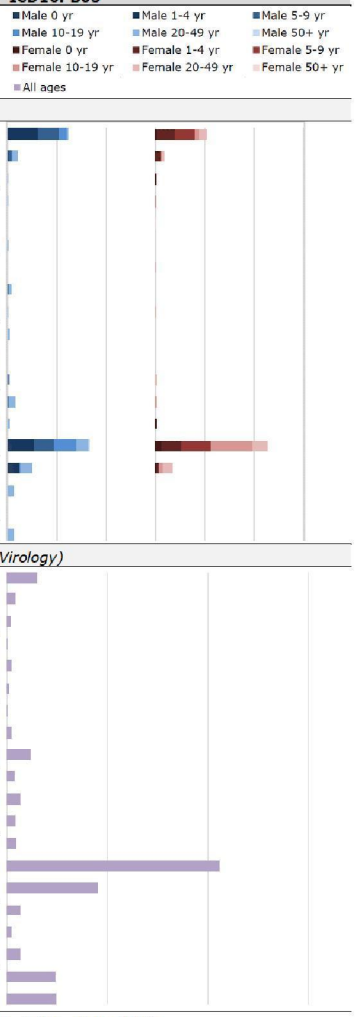
**Preliminary figures

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
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**	
2019*	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**	
2019	4	15	17	10	37	1	**84**	

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

Measles — **ICD9: 055** **ICD10: B05**

Year	Age (years)						Total
	[illegible]	10)(2e)	10)(2e)	(10)(2e)	(10)(2e)	10)(2+	
Hospitalisations (source: Prismant/DHD/CBS)*							
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							**91**
2015							**13**
2016							**5**
2017							**13**
2018							**48**
2019							**49**



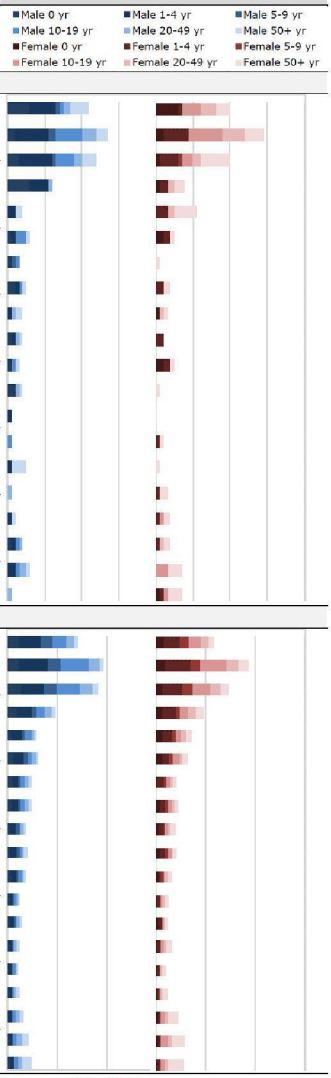
*Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

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

*Age is unknown for six patients.

Meningococcal disease — **ICD10: A39**

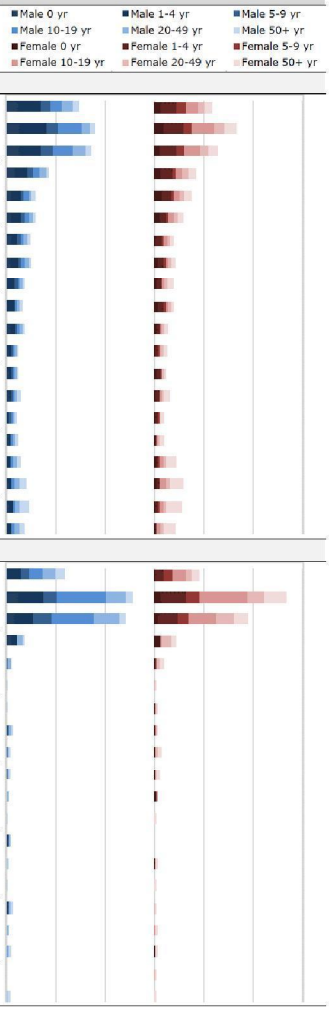
Year	Age (years)						Total
	0)(2e)	10)(2e)	10)(2e)	(10)(2e)	(10)(2e)	0)(2e)+	
Mortality (source: CBS)							
1997	7	13	6	6	2	7	**41**
1998	10	19	2	10	2	9	**52**
1999	9	13	4	7	4	11	**48**
2000	12	8	1	6	6	9	**42**
2001	4	16	2	16	10	8	**56**
2002	4	14	2	8	4	12	**44**
2003	7	7	0	0	3	3	**20**
2004	0	5	0	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**
2019*	1	1	0	1	1	4	**8**
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**
2019	5	20	5	26	38	67	**161**



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

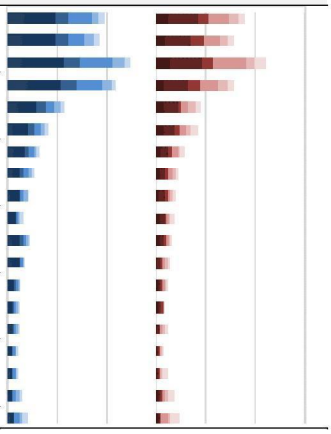
Meningococcal disease

Year	Age (years)						Total
	)(2e)	(10)(2e)	(10)(2e)	(10)(2e)	(10)(2e)	0)(2e)+	
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	0)(2e	0)(2e	(10)(2e
(10)(2e)	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**
2019	6	19	5	27	34	68	**159**
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**
2019	0	0	0	0	1	5	**6**



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
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**	
2019	1	2	1	7	14	37	**62**	
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	0)(2	(10)(2e	
(10)(2e)	0)(2	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	)(2	0)(2	0)(2	0)(2	10)(2e	
2014	8	16	9	9	8	11	**61**	
2015	9	11	5	14	8	18	**65**	
2016	14	12	)(2	0)(2	0)(2	0)(2	10)(2e	
2017	11	17	3	23	15	12	**81**	
2018	9	22	1	12	11	19	**74**	
2019	5	17	3	18	14	15	**72**	

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
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	0)i2	0)i2	**(10)i2e**	
(10)i2e	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^	15	20	10	20	30	35	**135**	
2017^	15	30	5	50	30	55	**180**	



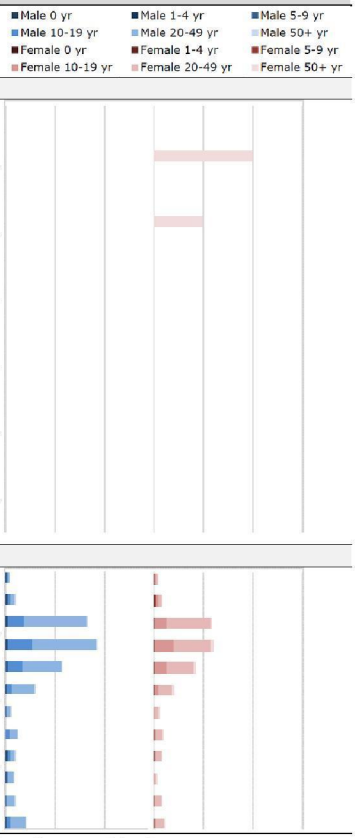
*Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

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

*Age is unknown for 12 patients.

Mumps — **ICD10: B26**

Year	Age (years)						Total
	)1[	10)(2e)	10)(2e)	(10)(2e)	(10)(2e)	0)(2+	
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**
2019*	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**
2019	0	4	3	22	95	7	**131**

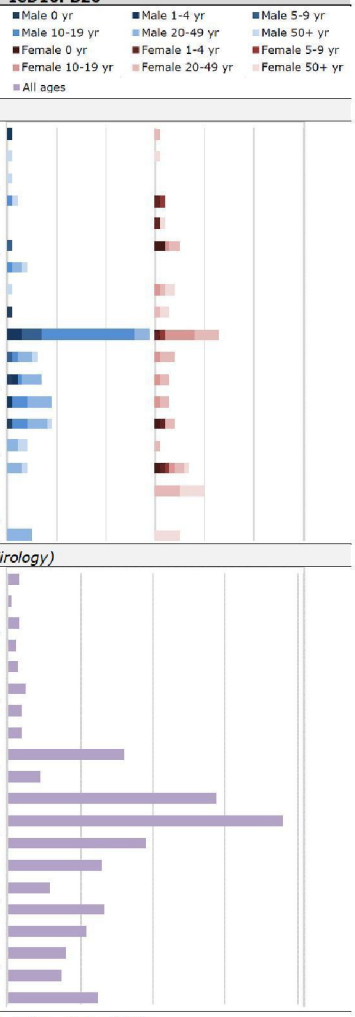


*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

**Notifiable from 1 December 2008 onwards

Mumps — **ICD9: 072** **ICD10: B26**

Year	Age (years)						Total
	)\2	10)\2e	10)\2e	(10)(2e)	(10)(2e)	0)(2+	
Hospitalisations (source: Prismant/DHD/CBS)*							
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							**29**
2015							**66**
2016							**54**
2017							**40**
2018							**37**
2019							**62**



*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.

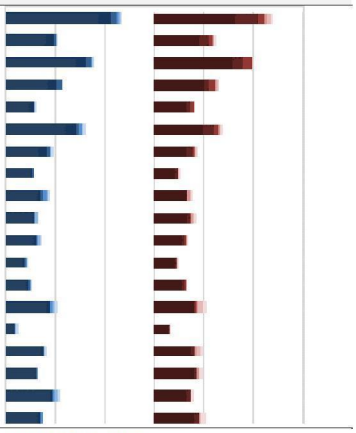
*Age is unknown for one patient.

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 to 4	5 to 9	10 to 19	20 to 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**	
2019*	2	0	0	0	0	0	**2**	
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**	
2019								

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

Pertussis — **ICD9: 033** **ICD10: A37**

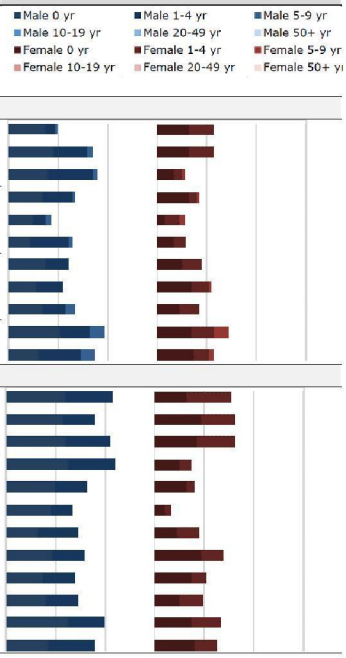
Year	Age (years)						Total
	<1	1-4	5-9	10-19	20-49	50+	
Hospitalisations (source: Prismant/DHD/CBS)*							
1999	351	73	24	12	8	4	**472**
2000	171	37	12	5	0	5	**230**
2001	301	40	32	1	2	2	**378**
2002	188	24	23	4	3	3	**245**
2003	114	14	9	2	0	1	**140**
2004	221	42	13	10	3	12	**301**
2005	131	28	11	5	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^	140	10	0	10	5	10	**175**
2016^	155	15	0	5	5	10	**190**
2017^	150	10	0	10	0	10	**180**



*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 three patients.

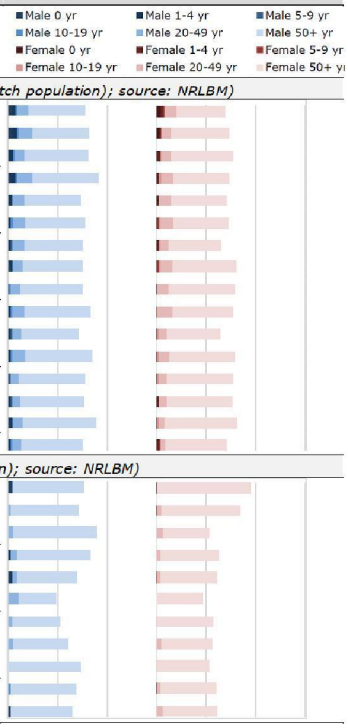
Pneumococcal disease

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**
2019	27	23	8	1			**59**
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**
2019	33	28					**61**



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**
2019	9	13	3	4	61	503	**593**
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	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
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**	
2019*	0	0	0	0	0	16	**16**	
*Hospitalisations pneumococcal pneumonia** (source: Prismant/DHD/CBS)*								
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	305	2,175	**2,525**	
2016^	0	5	5	20	380	2,125	**2,540**	
2017^	5	5	5	15	270	2,180	**2,485**	

*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.

**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
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**	
2019*	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**	
2019	0	0	0	0	0	0	**0**	

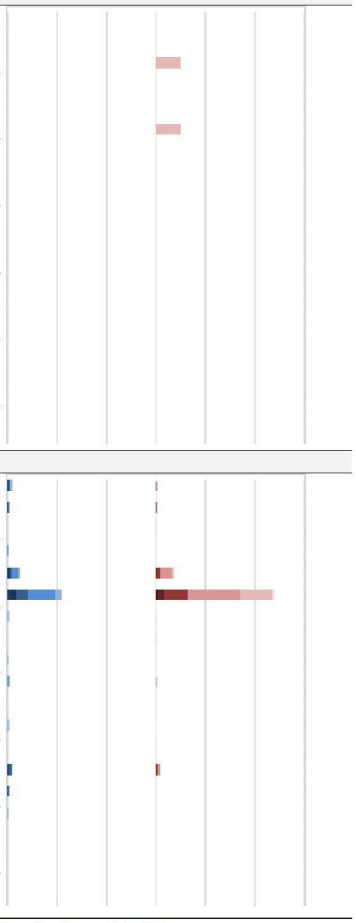
*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

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
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	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.

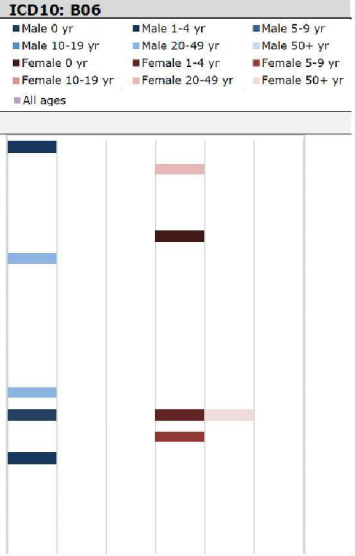
Rubella (acquired)								ICD10: B06
Year	Age (years)						Total	Male 0 yr / Male 1-4 yr / Male 5-9 yr / Male 10-19 yr / Male 20-49 yr / Male 50+ yr / Female 0 yr / Female 1-4 yr / Female 5-9 yr / Female 10-19 yr / Female 20-49 yr / Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	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**	
2019*	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**	
2019	0	0	0	0	0	0	**0**	

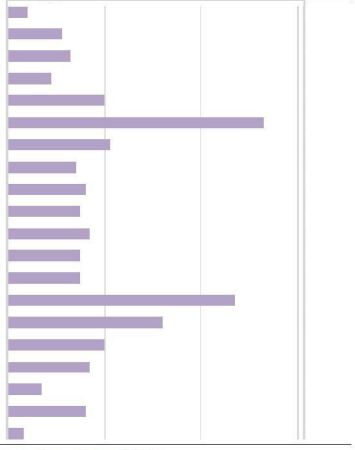


*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

Rubella (acquired) — **ICD9: 056** **ICD10: B06**

Year	Age (years)						Total
	[illegible]	10)(2e)	10)(2e)	(10)(2e)	(10)(2e)	10)(2+	
Hospitalisations (source: Prismant/DHD/CBS)*							
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							**32**
2015							**20**
2016							**17**
2017							**7**
2018							**16**
2019							**3**





*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.

** 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	■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
	1(2)	10(2e)	10(2e)	(10)(2e)	(10)(2e)	10(2e)+		
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**	
2019*	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**	
2019	0	0	0	0	0	0	**0**	

*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
	)|2	10)|2e	10)|2e	(10)(2e)	(10)(2e)	)|2 +		
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**	
2019*	0	0	0	0	0	0	**0**	

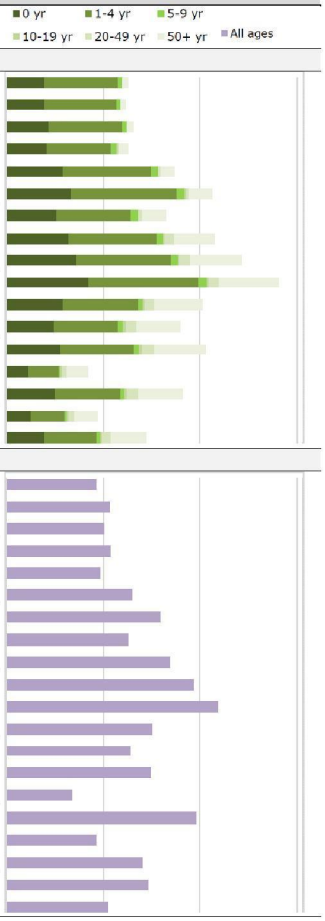
*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

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
Notifications (source: Osiris)*								
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	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	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	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	**189**	
2009	0	8	34	28	83	23	**176**	
2010	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	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**	
2019	0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	**164**	
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							**67**	
2016							**66**	
2017							**163**	
2018							**95**	
2019							**90**	

*Age is unknown for 25 patients.

Rotavirus

Year	Age (years)						Total
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	All ages
Hospitalisations (estimation; source: Prisman/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							**681**
2015							**1,957**
2016							**629**
2017							**1,407**
2018							**1,469**
2019							**1,054**



*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	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
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**	
2019*	0	0	0	0	0	3	**3**	
*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	0)(2	**10)(2e)**	
(10)(2e)	0)(2	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	105	15	10	50	70	**305**	
2016^	55	120	25	15	55	75	**345**	
2017^	70	120	25	10	50	60	**335**	

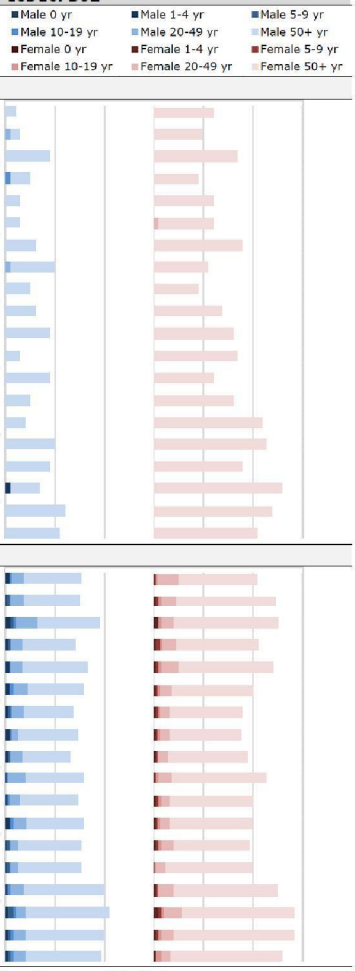
*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

**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.

Herpes zoster (shingles) — **ICD9: 053** **ICD10: B02**

Year	Age (years)						Total
	)(2	10)(2e	10)(2e	(10)(2e)	(10)(2e)	0)(2e+	
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**
2019*	0	0	0	0	0	32	**32**
*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	395	**495**
2016^	0	10	10	10	45	405	**480**
2017^	0	15	5	15	45	385	**470**

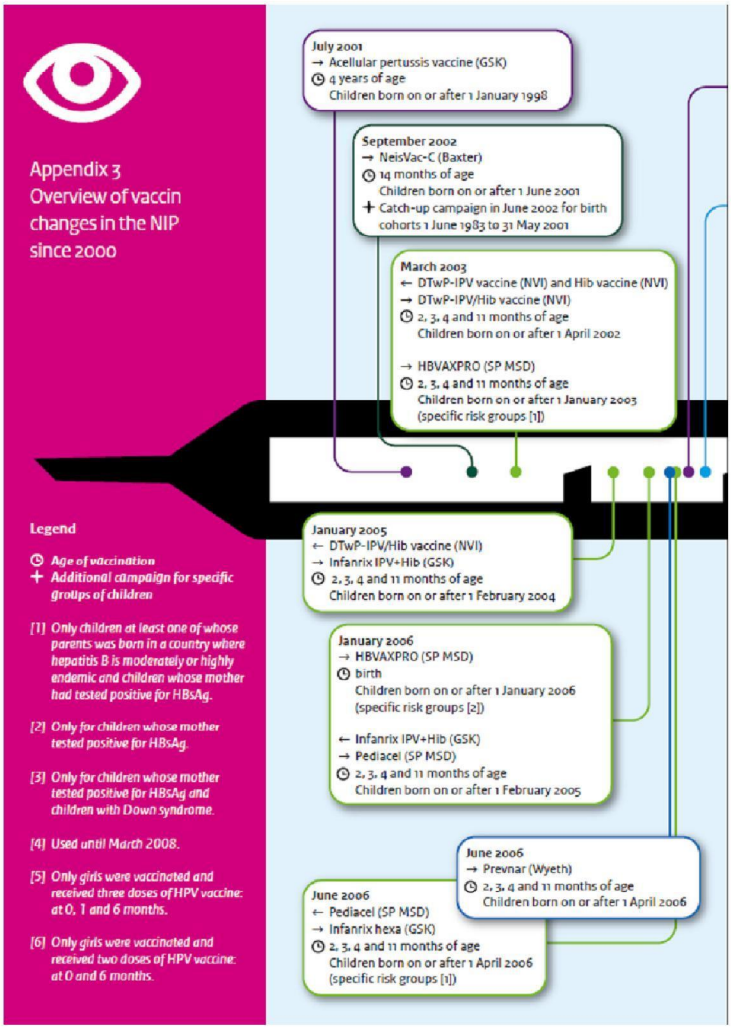


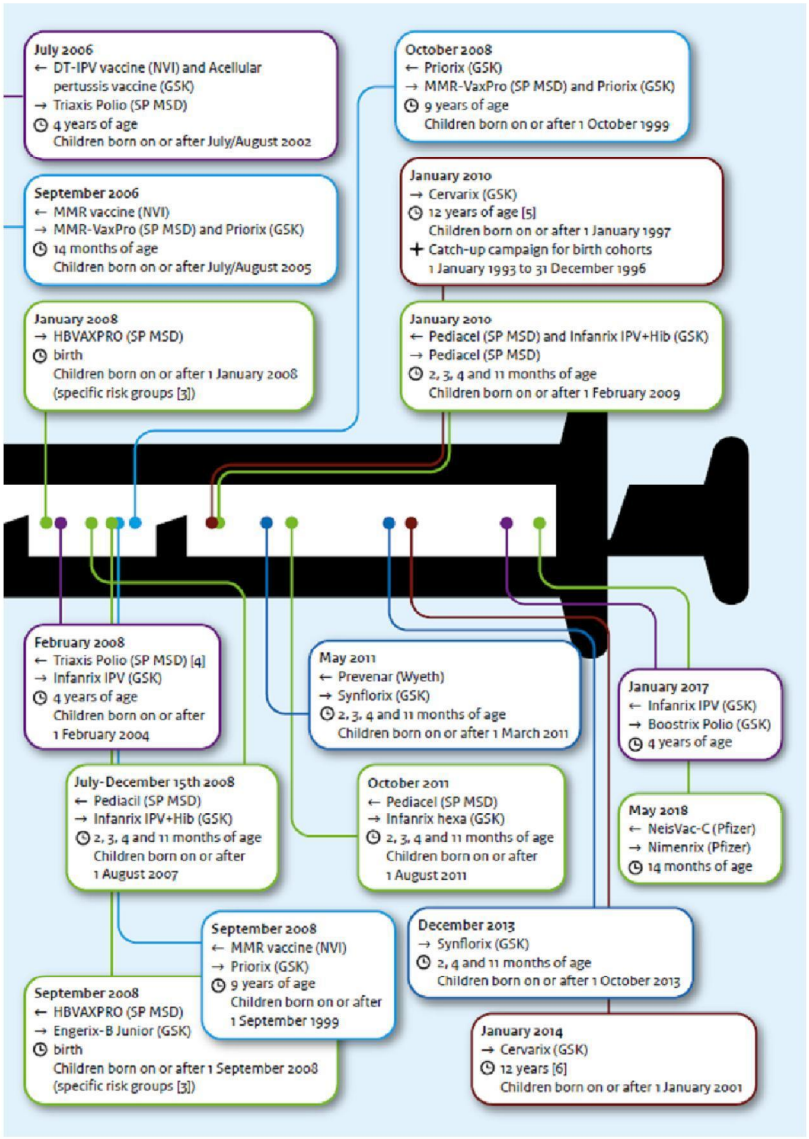
*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

**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.

Appendix 3 Overview of vaccine changes in the NIP from 2000




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
Boostrix / GSK RVG 35121 Diphtheria, tetanus and pertussis (acellulair component) vaccin (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
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
REVAXIS / SP RVG24534 Diphtheria, tetanus and inactivated poliomyelitis vaccine (absorbed; limited quantity of antigen(s)) 0.5 ml	Purified diphtheria-toxoid* > 2 IU Purified tetanus toxoid* > 20 IU Inactivated poliovirus type 1** 40 DU Inactivated poliovirus type 2** 8 DU Inactivated poliovirus type 3** 32 DU *adsorbed to aluminiumhydroxide 0.35 mg **produced on Verocells
Engerix-B Junior / GSK RVG24290 Hepatitis B vaccine (recombinant) 0.5 ml	Hepatitis B-virus surface antigen, recombinant* (S protein) absorbed 10 µg *produced on genetically engineered yeast cells (Saccharomyces cerevisiae)
HBVAXPRO / MSD RVG17316 Hepatitis B vaccine (rDNA) 0.5 ml	Hepatitis B virus surface antigen, recombinant (HBsAg)[1,2] 5 µg [1]Adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.25 mg Al+) [2]Produced in Saccharomyces cerevisiae (strain 2150-2-3) yeast by recombinant DNA technology

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.*
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 (01/07/2019 to 31/06/2020)

Vaccination coverage

1. van Lier EA, Kamp L, Oomen PJ, Giesbers H, van Vliet JA, Drijfhout IH, et al. Vaccinatiegraad en jaarverslag Rijksvaccinatieprogramma Nederland 2019. [Vaccination coverage and annual report National Immunisation Programme Netherlands 2019]. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2020 (RIVM report 2020-0011).
2. de Oliveira Bressane Lima P, van Lier A, de Melker H, Ferreira JA, van Vliet H, Knol MJ. MenACWY vaccination campaign for adolescents in the Netherlands: Uptake and its determinants. Vaccine. 2020;38(34):5516-24.

Acceptance of vaccination

1. Mollema L, Antonise-Kamp L, van Vliet J, de Melker H. Organisatorische en communicatieve interventies die de opkomst voor HPV-vaccinatie kunnen verhogen. JGZ Tijdschrift voor jeugdgezondheidszorg. 2019;51(3-4):101-5.

Burden of disease

1. Lagerweij GR, Schimmer B, Mooij SH, Raven CFH, Schoffelen AF, de Gier B, et al. State of Infectious Diseases in the Netherlands, 2019. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2020. RIVM report 2020-0048.

Adverse events

1. Nic Lochlainn LM, de Gier B, van der Maas N, Strebel PM, Goodman T, van Binnendijk RS, et al. Immunogenicity, effectiveness, and safety of measles vaccination in infants younger than 9 months: a systematic review and meta-analysis. Lancet Infect Dis. 2019;19(11):1235-45.

NIP-wide research topics

N.A.

Current NIP

Diphtheria

1. G. Berbers, P. van Gageldonk, J. van de Kassteele, U. Wiedermann, I. Desombere et al. Widespread ciriculation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries. Nature research 2020, Preprint 2020. DOI 10.21203/rs-35858/v1.

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

1. Schouls L, Schot C, De Voer RM, Van der Klis F, Knol M, Tcherniaeva I, et al. Lagging Immune Response to Haemophilus influenzae Serotype b (Hib) Conjugate Vaccine after the Primary Vaccination with Hib of Infants in The Netherlands. Vaccines. 2020;8(347).

Hepatitis B

1. Raven SFH, (10)(2e), Vossen (10)(2e) LG, Hautvast JLA, Roukens AHE, et al. Serological response to three alternative series of hepatitis B revaccination (Fendrix, Twinrix, and HBVaxPro-40) in healthy non-responders: a multicentre, open-label, randomised, controlled, superiority trial. Lancet Infect Dis. 2020;20(1):92-101.

Human papillomavirus (HPV) infection

1. Woestenberg PJ, van Benthem BH, Bogaards JA, King AJ, van der Klis FR, Pasmans H, et al. HPV infections among young MSM visiting sexual health centers in the Netherlands: Opportunities for targeted HPV vaccination. Vaccine. 2020.
2. Woestenberg PJ, Guevara Morel AE, Bogaards JA, Hooiveld M, van't Klooster TMS, Hoebe CJ, et al. Partial protective effect of bivalent HPV16/18 vaccination against anogenital warts in a large cohort of Dutch primary care patients. Clinical Infectious Diseases. 2020.
3. Vos RA, Pasmans H, Tymchenko L, Janga-Jansen AV, Baboe-Kalpoe S, Hulshof K, et al. High seroprevalence of multiple high-risk human papillomavirus types among the general population of Bonaire, St. Eustatius and Saba, Caribbean Netherlands. Vaccine. 2020;38(13):2816-26.
4. Man I, Vänskä S, Lehtinen M, Bogaards JA. Human papillomavirus genotype replacement: still too early to tell? The Journal of infectious diseases. 2020.
5. Pasmans H, Schurink-Van't Klooster TM, Bogaard MJ, van Rooijen DM, de Melker HE, Welters MJ, et al. Long-term HPV-specific immune response after one versus two and three doses of bivalent HPV vaccination in Dutch girls. Vaccine. 2019;37(49):7280-8.
6. Qendri V, Bogaards JA, Berkhof J. Pricing of HPV vaccines in European tender-based settings. The European Journal of Health Economics. 2019;20(2):271-80.
7. Qendri V BJ, Baussano I , Lazzarato F, Vänskä S, Berkhof J. The cost-effectiveness profile of sex-neutral HPV immunization in European tender-based settings. IPVC 2020; (conference abstract); Barcelona2020.
8. Woestenberg, P. J., King, A. J., Van Benthem, B. H., Leussink, S., Van der Sande, M. A., (10)(2e). J., ... & Medical Microbiological Laboratories and the Public Health Services. (2020). Bivalent vaccine effectiveness against anal human papillomavirus positivity among female sexually transmitted infection clinic visitors in the Netherlands. The Journal of Infectious Diseases, 221(8), 1280-1285.
9. Hoes, J., Pasmans, H., Knol, M. J., Donken, R., van Marm-Wattimena, N., Schepp, R. M., ... & de Melker, H. E. (2020). Persisting Antibody Response Nine Years after Bivalent HPV Vaccination in A Cohort of Dutch Women: Immune Response and the Relation with Genital HPV Infections. The Journal of Infectious Diseases.
10. Donken, R., Hoes, J., Knol, M. J., Ogilvie, G. S., Dobson, S., King, A. J., ... & de Melker, H. E. (2020). Measuring vaccine effectiveness against persistent HPV infections: a comparison of different statistical approaches. BMC Infectious Diseases, 20(1), 1-11.
11. Vos RA, Pasmans H, Tymchenko L, Janga-Jansen AVA, Baboe-Kalpoe S, Hulshof K, de Melker HE, van der Klis FRM. High seroprevalence of multiple high-risk human papillomavirus types

among the general population of Bonaire, St. Eustatius and Saba, Caribbean Netherlands. Vaccine. 2020 Mar 17;38(13):2816-2826. doi: 10.1016/j.vaccine.2020.02.017.

Measles

1. Bodewes R, Reijnen L, Zwagemaker F, Kohl R, Kerkhof J, de Swart R, et al. Verbeteren van moleculaire surveillance van mazelen in Nederland. Analyse. 2020;2:40-3.
2. Verberk JDM, Vos RA, Mollema L, van Vliet J, van Weert JWM, de Melker HE, et al. Third national biobank for population-based seroprevalence studies in the Netherlands, including the Caribbean Netherlands. BMC Infect Dis. 2019;19(1):470.
3. 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: Short-Term and Long-Term Decreases in Antibody Responses Among Children Vaccinated Before 12 Months of Age. J Infect Dis. 2019;220(4):594-602.
4. Nic Lochlainn LM, de Gier B, van der Maas N, van Binnendijk R, Strebel PM, Goodman T, et al. Effect of measles vaccination in infants younger than 9 months on the immune response to subsequent measles vaccine doses: a systematic review and meta-analysis. Lancet Infect Dis. 2019.
5. Nic Lochlainn LM, de Gier B, van der Maas N, Strebel PM, Goodman T, van Binnendijk RS, et al. Immunogenicity, effectiveness, and safety of measles vaccination in infants younger than 9 months: a systematic review and meta-analysis. Lancet Infect Dis. 2019.

Meningococcal disease

1. de Oliveira Bressane Lima P, van Lier A, de Melker H, Ferreira JA, van Vliet H, Knol MJ. MenACWY vaccination campaign for adolescents in the Netherlands: Uptake and its determinants. Vaccine. 2020;38(34):5516-24.
2. de Oliveira Bressane Lima P, van Lier A, de Melker H, Ferreira JA, van Vliet H, Knol MJ. MenACWY vaccination campaign for adolescents in the Netherlands: Uptake and its determinants. Vaccine. 2020.
3. van den Broek B, van Els C, Kuipers B, van Aerde K, Henriet SS, de Groot R, et al. Multi-component meningococcal serogroup B (MenB)-4C vaccine induces effective opsonophagocytic killing in children with a complement deficiency. Clin Exp Immunol. 2019;198(3):381-9.
4. 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.
5. 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. 2020 May 6;70(10):2036-2044.

Mumps

1. Bodewes, R., et al., Optimizing molecular surveillance of mumps genotype G viruses. Infect Genet Evol, 2019. 69: p. 230-234.

2. Bodewes, R., et al., Molecular epidemiology of mumps viruses detected in the Netherlands, 2017-2019. bioRxiv, 2020.
3. de Wit, J., et al., Identification of Naturally Processed Mumps Virus Epitopes by Mass Spectrometry: Confirmation of Multiple CD8+ T-Cell Responses in Mumps Patients. J Infect Dis, 2020. 221(3): p. 474-482.
4. Kaaijk, P., et al., A Third Dose of Measles-Mumps-Rubella Vaccine to Improve Immunity Against Mumps in Young Adults. J Infect Dis, 2020. 221(6): p. 902-909.

Pertussis

1. Lambert EE, Buisman AM, van Els CACM. Superior B. pertussis specific CD4+ T-cell immunity imprinted by natural infection. Adv Exp Med Biol.2019;1183:81-98. Review.
2. den Hartog G, Schijf MA, Berbers GAM, van der Klis FRM, Buisman AM. Bordetella pertussis induces IFN-γ production by NK cells resulting in chemo-attraction by respiratory epithelial cells. J Infect Dis. 2020 Mar 27:jiaa140.
3. Kroes MM, Mariman R, Hijdra D, Hamstra HJ, van Boxtel KJWM, van Putten JPM, de Wit J, Pinelli E. Activation of Human NK Cells by Bordetella pertussis Requires Inflammasome Activation in Macrophages. Front Immunol. 2019 Aug 27;10:2030.
4. G. Berbers, P. van Gageldonk, J. van de Kassteele, U. Wiedermann, I. Desombere et al. Widespread ciriculation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries. Nature research 2020, Preprint 2020. DOI 10.21203/rs-35858/v1.
5. Lambert EE, Corbière V, van Gaans-van den Brink JAM, Duijst M, Venkatasubramanian PB, Simonetti E, Huynen M, Diavatopoulos DD, Versteegen P, Berbers GAM, Mascart F, van Els CACM. Uncovering distinct primary vaccination-dependent profiles in human Bordetella pertussis specific CD4+ T-cell responses using a novel whole blood assay. Vaccines. 2020 May 15;8(2):E225.

Pneumococcal disease

1. Van de Garde MDB, Knol MJ, Rots NY, van Baarle D, van Els CACM. Vaccines to Protect Older Adults against Pneumococcal Disease. Interdiscip Top Gerontol Geriatr. 2020;43:113-130.

Poliomyelitis

N.A.

Rubella

1. Verberk, J.D.M., et al., Third national biobank for population-based seroprevalence studies in the Netherlands, including the Caribbean Netherlands. BMC Infect Dis, 2019. 19(1): p. 470.

Tetanus

1. G. Berbers, P. van Gageldonk, J. van de Kassteele, U. Wiedermann, I. Desombere et al. Widespread ciriculation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries. Nature research 2020, Preprint 2020. DOI 10.21203/rs-35858/v1.

Potential NIP target diseases

Hepatitis A

N.A.

Respiratory syncytial virus

1. Reeves RM, van Wijhe M, Tong S, Lehtonen T, Stona L, Teirlinck AC, et al. Respiratory Syncytial Virus-Associated Hospital Admissions in Children Younger Than 5 Years in 7 European Countries Using Routinely Collected Datasets. J Infect Dis. 2020 Aug 20:jiaa360.
2. van Boven M, Teirlinck AC, (10)(2e), Hooiveld M, van Dorp CH, Reeves RM, et al. Estimating Transmission Parameters for Respiratory Syncytial Virus and Predicting the Impact of Maternal and Pediatric Vaccination. J Infect Dis. 2020 Aug 21:jiaa424.
3. Schepp, R. M., et al. Development and Standardization of a High-Throughput Multiplex Immunoassay for the Simultaneous Quantification of Specific Antibodies to Five Respiratory Syncytial Virus Proteins. mSphere 2019;4(2).
4. G. Berbers, L. Mollema, F. van der Klis, G. den Hartog, R. Schepp. Antibody responses to Respiratory Syncytial Virus: a cross-sectional serosurveillance study in the Dutch population with emphasis on infants up to 2 years and COPD patients. Accepted.
5. van Erp EA, Lakerveld AJ, de Graaf E, et al. Natural killer cell activation by respiratory syncytial virus-specific antibodies is decreased in infants with severe respiratory infections and correlates with Fc-glycosylation. Clin Transl Immunology. 2020;9(2):e1112. Published 2020 Feb 19.

Rotavirus

N.A.

Varicella zoster virus (VZV) infection

1. van Lier A. Epidemiology of varicella zoster virus in the Netherlands: implications for vaccination strategies [dissertation]; 2019.
2. Vos RA, Mollema L, van Boven M, van Lier A, Smits G, Janga-Jansen AVA, et al. High varicella-zoster virus susceptibility in Caribbean island populations: implications for vaccination. Int J Infect Dis. 2020;94:16-24.
3. van Lier EA, van der Maas NAT, de Melker HE. Varicella in the Netherlands: Background information for the Health Council. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu (RIVM); 2020 (RIVM rapport 2019-0197).
4. van Kampen JJA, Bruns AHW, E. vL, Koelewijn JM, Ruijs WLM, Komen DJC, et al. Herziene multidisciplinaire richtlijn 'Varicella': ruimere indicatie voor postexpositieprofylaxe. Ned Tijdschr Geneeskd. 2020;164:D5380.

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 2019:
https://www.rivm.nl/publicaties/vaccinatiegraad-en-jaarverslag-rijksvaccinatieprogramma-nederland-2019

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 Grieppreventie (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/bibliotheek/rapporten/2019-0079.pdf

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/bibliotheek/rapporten/2019-0079.pdf

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